Transparency in Risk Regulation
The Case of the European Medicines Agency

Way, Dominic

Awarding institution:
King's College London

Transparency in Risk Regulation: The Case of the European Medicines Agency

2017

Dominic Hugo Patrick Way
King's College London
Doctor of Philosophy in Geography (Science) Research FT

Dedicated in loving memory of my grandfather,
Peter Orchard Williams CBE FRCP (1925-2014)

ABSTRACT

Transparency has risen to prominence in risk regulation leading government authorities in Europe and North America to introduce an *avalanche* of new policies. While transparency promises to achieve many instrumental objectives, there is insufficient empirical evidence on the effectiveness of the actual policies being implemented. This study first explored the ambiguity of transparency in risk regulation. This informed a review of the seriously fragmented literature and an original typology, which clarified what is being made transparent by risk regulators (objects), how (mechanisms), why (goals) and for whom (audiences). An in-depth case study was then conducted on transparency at the European Medicines Agency (EMA), the EU agency responsible for pharmaceuticals. The four case methods were extensive historical and contemporary documentation; direct observations and interviews conducted between 2012 and 2016; and multi-national surveys (UK, France, Germany, Spain) of medical doctors (specialists and general practitioners) and patients diagnosed with one of five medical conditions (HIV/AIDS, idiopathic pulmonary fibrosis, multiple sclerosis, rheumatoid arthritis, osteoporosis) (N=2,015). After providing an in-depth historical analysis of transparency at EMA (1995-2016), the case study evaluated three salient policies, which all seek to make the data that underpins decision-making in EMA's scientific committees more 'visible' to outsiders.

EMA's policies have important strengths and weaknesses for achieving the regulator's objectives. Transparency was also found to have serious unwanted effects including significantly increasing legal action against EMA, enabling unrestricted (high and low quality) re-analyses of benefit-risk data, and consuming substantial agency resources. Simply publishing large quantities of raw data online is unlikely to be the most effective way of achieving the regulator's transparency objectives. Rather, *effective* transparency requires understanding (1) the limits of full disclosure, (2) the desired quality of transparency (for multiple audiences), (3) the capacity of expert and non-expert audiences to assess transparent information, and (4) the ability of intermediaries to re-package and communicate benefit-risk information effectively. Choosing the right transparency policies ultimately means resisting becoming captivated by quantity and must take opportunity costs into careful consideration. The thesis concludes by strongly arguing that transparency should be re-conceptualised as a (risk) communication process in order to improve policy effectiveness.

ACKNOWLEDGEMENTS

First and foremost I would like to thank Ragnar Löfstedt, my primary supervisor, who provided me with tremendous academic support over the past four and a half years. My PhD simply would not have been possible without his invaluable guidance. I extend my thanks to Henry Rothstein, my secondary supervisor, who gave me precious advice and recommendations especially on earlier drafts of this thesis. I would like to express my great appreciation to Frederic Bouder (Maastricht University) and Darrick Evensen (Cardiff University) whose expertise especially on transparency, pharmaceutical regulation and survey methodologies helped guide my research. I wish to acknowledge David Demeritt and all the PhD students that contributed to King's College London's Hazards and Risk reading groups. I would also like to thank my viva examiners, Julie Barnett (Bath University) and George Gaskell (London School of Economics).

In collecting data for this thesis, it is a pleasure to thank David Haerry and all the patient group organisations that generously provided their time and assistance including (alphabetically): Asociación De Familiares Y Enfermos De Fibrosis Pulmonar Idiopática; Association Fibrose Pulmonaire Idiopathique; British Lung Foundation; Esclerosis Multiple Espana; European AIDS Treatment Group; Liga Reumatológica Española; Multiple Sclerosis Society; and Pulmonary Fibrosis Trust. The funding for collecting the survey data was provided by a grant from Biogen Idec. and I would particularly like to thank Carmen Bozic, James Milligan and Jan Kilhamn. I am also grateful to the staff at Ipsos, who collected and collated the survey data, and I wish to acknowledge the help I received from EMA regulators with special thanks to Juan Garcia.

Finally, I am deeply grateful and indebted to my family and loved ones, Judy, Patrick, Oliver, Frederick, Jess, Alastair and Simone, for their unwavering support and encouragement throughout.

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ACRONYMS

ABPI	Association of the British Pharmaceutical Industry
AEMPS	Spanish Agency for Medicines and Healthcare Products
ANSM	National Agency for the Safety of Medicine and Health Products
BfArM	Federal Institute for Drugs and Medical Devices
BMA	British Medical Association
BMJ	British Medical Journal
BSE	Bovine Spongiform Encephalopathy
CEO	Corporate European Observatory
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical Study Report
DG-SANTE	Director General for Health and Food Safety
DKMA	Danish Medicines Agency
EATG	European AIDS Treatment group
ECCO	European Crohn's and Colitis Organisation
ECHA	European Chemicals Agency
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EFSPI	The European Federation of Statisticians in the Pharmaceutical Industry
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC	The European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EU	European Union
EU-CTR	European Union Clinical Trials Register
EUnetHTA	European Network for Health Technology Assessment
FDA	US Food and Drug Administration
FEAM	Federation of European Academies of Medicines
FOI	Freedom of Information
FSIS	US Food Safety and Inspection Service
GCGMA	Drug Commission of the German Medical Association

HSE	UK Health and Safety Executive
HTA	Health Technology Assessors
IAPA	The International Alliance of Patients' Organisations
IAPO	International Alliance of Patient Organisations
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
IFAH-Europe	International Federation for Animal Health Europe
IPF	Idiopathic Pulmonary Fibrosis
IQWiG	Germany Institute for Quality and Efficiency in Healthcare
ISDB	International Society of Drug Bulletins
MEP	Member of European Parliament
MHRA	Medicines and Healthcare Products Regulatory Agency
MRCT	Multi-Regional Clinical Trials Center at Harvard University
MS	Multiple Sclerosis
NCA	National Competent Authority
NGO	Non-Governmental Organisation
NHS	UK National Health Service
NICE	UK National Institute for Health and Care Excellence
NRC	US National Research Council
PhRMA	Pharmaceutical Research and Manufacturers of America
PRAC	Pharmacovigilance Risk Assessment Committee
PhUSE	The Pharmaceutical Users Software Exchange
RA	Rheumatoid Arthritis
RAPIM	Romanian Association of International Medicines Manufacturers
SmPC	Summary of Product Characteristics
TRI	Toxics Release Inventory
UK	United Kingdom
WHO	World Health Organisation

Chapter I: INTRODUCTION

> *"We [at the European Medicines Agency] believe that patients have a right to know about the scientific basis for the approval and use of their medicines and that transparency of clinical trial data is therefore essential"* (Bonini, Eichler, Rasi, Wathion, 2014).
>
> *"One thing is certain, transparency is crucial to [the European Food Safety Authority's] work as we know that it is intimately linked with trust in the risk assessment process and hence the value of our work for citizens"* (Url, 2013).

These clear commitments to 'transparency' from four of the most senior European Medicines Agency (EMA) regulators[1] and the European Food Safety Authority's (EFSA) Executive Director, Bernhard Url, are not unique. Rather, transparency has become *de rigueur* in the regulation of risk (Hood and Heald, 2006; O'Neill, 2006; Etzioni, 2010), defined as "government interference with market or social processes to control potential adverse consequences to health" (Hood *et al*. 2001). A multiplicity of regulatory authorities, committees and other bodies in the US, Canada, Europe and beyond have sought to enhance transparency so that, broadly speaking, "outsiders can observe what is going on inside the organisation" (Heald, 2006a). This has been especially true in policy domains related to health, the environment, and safety (Shrader-Frechette, 1991; Löfstedt and Bouder, 2014; Rothstein *et al*. 2016). Examples of such organisations are numerous. They range from those operating at the supranational EU level such as EMA, EFSA and the European Chemicals Agency (ECHA) (Rasi, 2016; Url, 2013; ECHA, 2017), to national-level organisations such as the United Kingdom (UK) Health and Safety Executive, the US Food and Drug Administration (FDA), and Health Canada (Lexchin and Mintes, 2004; Chakraborty and Löfstedt, 2013), as well as an array of ad hoc committees and other public bodies[2] (e.g. the Dutch Gezondheidsraad and the US National Research Council) (Bijker *et al*. 2009). Collectively they have introduced what can be described as an *avalanche* of new policies designed to enhance transparency.

Few would argue with the point that transparency is in principle a good idea (Trachtenberg, 2015). Maintaining and strengthening transparency is viewed as a modern day essential with many stressing that the public have a right to know how risks to their health and the

[1] Sergio Bonini (Senior Medical Officer), Hans-Georg Eichler (Senior Medical Officer), Nöel Wathion (Deputy Director) and Guido Rasi (3rd Executive Director).

[2] To be clear, risk is regulated in a complicated multi-level governance system where regulatory bodies are characterised by overlapping jurisdictions and multi-actor alliances (*see* Renn *et al*. 2011).

environment are regulated (Stiglitz, 2003; Naurin, 2006; Fung, 2013). Others have emphasised that transparency can contribute to a strong democracy (Piotrowski and Borry, 2010; Tan, 2014) and should be viewed as an ethical obligation or even a human right (Birkinshaw, 2006). Although there are organisations that seek to enhance transparency – such as the eponymously named 'Transparency International' – there "does not seem to be any organisation whose *raison d'être* is to decrease transparency" (O'Connor, 2016: 2). Transparency is also often seen as the inverse of secrecy, dishonesty and cover-up (Black, 1997; Birchall, 2011). For example, a lack of transparency implies the regulators are "purposefully withholding information that would otherwise be in the public domain" (Löfstedt and Way, 2016a: 1) and gives rise to suspicions about the regulators (Stiglitz, 2002; Grigorescu, 2007; Birchall, 2011), as well as their legitimacy (Zurn, 2004; De Fine Licht *et al*. 2014).

The concept has also been associated with the notion of 'good governance' and an array of instrumental public policy objectives (Hood and Heald, 2006; Pollitt and Bouckaert, 2011). As the former Supreme Court Justice, Louis Brandeis, famously commented in the early 20th Century:

> *"Publicity is justly commended as a remedy for social and industrial diseases. Sunlight is said to be the best of disinfectants; electric light the most efficient policeman"* (Brandeis, 1913).

More recently, multiple instrumental goals for transparency have been put forward by academics, policymakers, and other influencers (Meijer *et al*. 2015; Löfstedt and Way, 2016a). These include arguments that transparency can strengthen the information position of citizens, enable meaningful public participation (Stiglitz, 1999), improve the quality of risk regulation, and prevent regulatory capture (Carpenter and Moss, 2013; Dudley and Weigrich, 2015), as well as induce industry to adopt less risky behaviour (Fung *et al*. 2007; Weil *et al.* 2013) and build public trust in risk regulation (Frewer *et al*. 2003; Grimmelikhuijsen, 2010; Löfstedt *et al*. 2011). For example, one argument is that information about regulatory authorities (e.g. decisions, actions and deliberations) needs to be made available so that outsiders can determine whether they are acting in the public's interest or not (Grigoescu, 2007). Transparency is thus viewed very highly by many or as Christopher Hood (2006a: 3) comments: "transparency is a term that has attained quasi-religious significance in debate over governance and institutional design".

Yet, despite the importance placed on transparency, few studies have critically examined the effectiveness of the risk regulators' various transparency policies (Löfstedt, 2013). No one currently knows whether the actual policies initiated have been (or will be) effective or not in achieving their intended public policy objectives (Etzioni, 2010). There is clearly an important difference between expecting a transparency policy will achieve a desired effect and determining whether it has actually done so (*see* Coglianese, 2012 for a discussion). In turn, a growing literature has emphasised that measuring and evaluating the effectiveness of transparency policies, in different contexts, is essential (Heald, 2003, 2006a, 2006b; Etzioni, 2010; Coglianese, 2012; Löfstedt, 2013; Gupta and Mason, 2014; Trachtenberg, 2015). Emerging findings from outside risk regulation have now shown that policies designed to enhance transparency can indeed have positive effects, although they will not necessarily do so, can have severe unwanted effects, and must be balanced against important trade-offs (e.g. resource consumption and opportunity costs) (Hood, 2001; Hood and Heald, 2006; Grimmelikhuijsen, 2010, 2012; Gupta and Mason, 2014). However, few studies have been conducted in the field of risk regulation. What is needed is a more sophisticated understanding of transparency in risk regulation and a critical assessment of the policies introduced by the regulators in achieving their intended public policy outcomes.

This PhD thesis provides an exploration and critical examination of transparency in risk regulation, while paying particular attention to the European pharmaceutical policy domain. In so doing, the thesis critically examines the effectiveness of the transparency policies introduced by one risk regulator, namely, the EMA and addresses the question:

> *How effective have the European Medicines Agency's input transparency policies been in achieving its public policy objectives?*

The rest of this introductory chapter proceeds as follows. First, the chapter explains that transparency is an ambiguous concept and can take many different forms in risk regulation alone (section 1.1). In order to answer the research question, clarity over these forms is thus much needed. This includes distinctions between what is being made transparent, how, why and for whom (Gupta and Mason, 2014). A key research objective is therefore to offer an original typology of transparency that can be used to analyse and compare different policies. Second, the chapter explains how the 'effectiveness' of transparency policies will be measured and evaluated in this thesis (section 1.2). In particular, transparency is valued instrumentally

(rather than intrinsically) and effectiveness means that individuals are able to receive, process, digest and use the 'transparent' information made available by the regulators (Heald, 2003, 2006a, 2006b). Third, the chapter briefly elaborates on the EMA's regulatory responsibilities as well as its most notable transparency policies (section 1.3). This includes a justification for why the EMA provides an important (and interesting) case for examining the concept of transparency in risk regulation. Fourth, the chapter outlines how the rest of this thesis is organised (section 1.4).

(1.1) Transparency policies

The first component of the research question that requires elaboration centres on: 'What exactly are transparency policies?' Clarifying key concepts and definitions is critical for evaluating the effectiveness of any policy, regulation, or other intervention (Coglianese, 2012). However, a key issue with transparency is that it is an ambiguous concept that is often defined with little rigour (Florini *et al*. 1999; Michener and Bersch, 2016). Despite frequently being used and advocated in public speeches and official documents, the term "is more often invoked than defined" (Hood, 2006a: 3). Broad definitions and metaphors are commonly used such as "lifting the veil of secrecy" (Davis, 1998: 121) or "making the invisible visible" (Hillebrandt *et al*. 2014: 4). Perhaps a more useful one attempts to make clearer what is being made visible:

> *"[Transparency is] the conduct of [regulation] in a fashion that makes decisions, rules and other information visible from the outside"* (Hood, 2010: 989).

The main issue with all of these definitions, however, is that they are too vague and do not help analysts distinguish between different forms and divergent meanings (Langley, 2001: 75-77). As Gupta and Mason (2014b: 5) put it: "An association of transparency with visibility leaves aside […] what is being made visible, by whom, and for whom; the desired quality and/or quantity of transparency; and the (governance) *effects* expected to flow from it" [italics in original]. This ambiguity has caused confusion in the literature and policymaking or what Meijer *et al*. (2015) describe as "dialogues of the deaf".

The ambiguity of transparency has been dealt with in at least three main ways in the now extensive multi-disciplinary literature (Gupta and Mason, 2014). First, some authors have lamented the lack of a shared definition (Etzioni, 2010; Seidman, 2011). For example, Etzioni

(2010) argues that transparency is an overrated concept that suffers from a distinct lack of empirical analysis and critical discussion over its meaning. Second, some authors have sought to unpack the normative and political underpinnings of the concept (Gartsen and De Montoya, 2008; Birchall, 2011). For example, Birchall (2011) discusses the relationship between transparency and secrecy arguing that tensions between the two terms need to be addressed (e.g. secrecy can be desirable and beneficial). Third, several authors have developed transparency policy frameworks and typologies (Lodge, 2004: 129; Heald, 2006a; Prat, 2006; Coglianese, 2009; Mitchell, 2011; De Fine Lincht *et al*. 2014; Gupta and Mason, 2014; Meijer *et al*. 2015). Two approaches have been widely used by transparency scholars and are particularly relevant to this thesis. Heald (2006a) sketches out an anatomy of transparency that distinguishes between what is being made transparent (i.e. the objects of transparency). Meijer *et al*. (2015: 1) provide an interpretative framework and helicopter view that seeks to "guide and structure assessments of government transparency". Both of these approaches have provided much needed sophistication to analysing government transparency policies and distinguishing between different forms (*see* Cuccinielo *et al*. 2017). Yet, neither of these approaches, nor those adopted by other scholars, can be *directly* applied to risk regulation, at least without being adapted.

Thus what is needed is a transparency typology that can distinguish between different forms in risk regulation (Chapter II). Offering such a typology can serve at least two main purposes. First, a typology is necessary for evaluating the effectiveness of different transparency policies introduced in various regulatory contexts. Bringing sophistication into the debate can help scholars, as Hood (2007: 195) puts it:

> *"…move away from a banal view of transparency (that is, positive but unexamined) to a world of 'transparency with adjectives', in which trade-offs appear and the different adjectival forms of transparency can come into conflict".*

Developing a typology is therefore essential for answering this thesis's research question. Second, a typology can be used by other researchers and practitioners examining the concept. In particular, it promises to bring clarity and structure to the often disjointed debates on the effectiveness of policies initiated in different policy domains and regulatory contexts. For example, evaluations of transparency policies in areas ranging from food safety and pharmaceuticals to chemicals and the environment can be compared. Indeed, comparisons

between the evaluations made in this thesis (Chapter VIII) can be made in future research (e.g. studies examining other regulatory bodies).

(1.2) Evaluating effectiveness

The second component of the research question centres on how transparency might be valued, evaluated, and measured in this thesis. A burgeoning literature has sought to examine transparency for having an instrumental value (Meijer *et al*. 2015; Cucciniello *et al*. 2017). Researchers have sought to answer important questions such as: "How can transparency be best implemented?" or "What are the effects of various transparency policies?" (Hillebrandt *et al*. 2014). For example, De Fine Licht (2014) experimentally tested the effects of transparency on generating legitimacy and found that a straightforward positive correlation is naïve. Instrumental approaches notably contrast with a second strand of the literature that has taken an intrinsic approach, which views transparency as "an end in itself" (Dror, 1999; Hood, 2006b; O'Neil, 2006; Florini, 2007; Etzioni, 2010). For example, Birkinshaw (2006: 55-56) debates whether transparency should be elevated to human rights status (i.e. the right-to-know) based on "the protection for individuals against inefficient, oppressive or even bullying government". Although intrinsic approaches have provided rich debate, this thesis adopts an instrumental approach to valuing transparency and follows David Heald's argument that "elevating transparency to an intrinsic value should be resisted" (*see* Heald, 2003, 2006b, 2006b for a discussion).

A second question centres on how transparency policies might be evaluated instrumentally in this thesis. While many authors have debated how regulatory policies more generally might be evaluated (e.g. regulations, policies, tools or processes) (Jacobzone *et al*. 2007; OECD, 2009), some have specifically discussed transparency policy evaluations (Hood, 2006b; Etzioni, 2010; Coglianese, 2012; Cucciniello *et al*. 2017). For Coglianese (2012: 12), instrumental "evaluation[s] answer […] the question of whether a treatment" (e.g. a transparency policy or collection of policies) "works in terms of reducing a problem". For example, if a transparency policy seeks to build public trust then measuring changes to public trust that were caused by that policy would provide an ideal approach (although doing so may not necessarily be feasible).

Furthermore, Coglianese (2012) identifies three main types of evaluation: regulatory administration, behavioural compliance, and outcome performance. Regulatory administration studies relate to the "activity or delivery" of a transparency policy (e.g. How well have the regulators implemented a transparency policy?) (ibid, 2012). Behavioural compliance studies relate to whether behaviour complies with certain regulatory or policy standards (e.g. what level of compliance with transparency policies has there been from targeted actors?). Outcome performance studies relate to the actual effects of a transparency policy and whether changes in behaviour result in the regulators' desired outcomes (e.g. what were the outcomes of the transparency policy compared to the regulators intended goals?) (ibid, 2012). Although regulatory administration and behavioural compliance studies are important, evaluating the resulting outcomes of a transparency policy is "what matters most" (ibid, 2012). In other words, different transparency policies will have "differential effects on the achievement of public policy objectives" (Heald, 2012: 30) and evaluating whether the regulators' policies have achieved these objectives is of central importance (Coglianese, 2012). This thesis therefore focuses on outcome performance for evaluating regulatory transparency policies instrumentally.

Two main approaches to evaluating outcome performance instrumentally have been adopted in the transparency literature, namely: 'nominal' and 'effective' measurements (Heald, 2006a). Nominal measures of transparency might involve creating an index, league table or proxy of some sort (Relly and Sabharwal, 2009; Heald, 2006a). Examples include Alt and Lassen's (2006) index of institutional fiscal transparency, Transparency International's (2017) Corruption Perceptions Index, and the World Bank's Economic and Institutional Transparency Index and Political Transparency Index (Naurin and Lindstedt, 2010). Indeed, this approach has been particularly popular in finance and banking (Alt *et al*. 2002; Siklos, 2010; Heald, 2012; Hollyer *et al*. 2014) but is by no means limited to this domain (e.g. Finel and Lord, 1999). One main advantage of nominal measurements is that they can provide simple, generalised and actionable information that lends itself to policymaking (Mustafa *et al*. 2011). Researchers have therefore spent a great deal of time creating more comprehensive nominal measures, making suggestions for improving statistical analyses and promoting their own indices (e.g. Ko and Samajdar, 2010). However, the main issue with nominal measures is that they do not provide a measure of the *effectiveness* of the regulators' transparency policies. In particular, several authors have emphasised that there is a clear distinction between the two (e.g.

Forssbaech and Oxeheim, 2015), which Heald (2006a) refers to as the "transparency illusion". This occurs when one index or another may show that transparency is appearing to increase, but the reality is actually very different (ibid, 2006).

The central argument is that "for transparency to be effective, there must be receptors capable of processing, digesting and using the information" made available (ibid, 2006: 35; Michener and Bersch, 2016). There are many reasons why this criterion may not be met thus limiting the usefulness of nominal measures (*see* e.g. Roberts, 2006: 111-119). This includes information recipient overload (e.g. due to data dumping); the insufficient timeliness of information provision (e.g. receiving information after a decision has been made); misleading or inaccurate information (e.g. poor record keeping); changes to the effectiveness of policies over time; governments spinning unfavourable information (e.g. window dressing); and individuals being ill-equipped to interpret the transparent information (e.g. due to time, resources or expertise) (Roberts, 2006: 111-119; Gupta and Mason, 2014). For example, if the objective of a transparency policy is to inform the 'lay' public about the rationale for coming to a regulatory decision, then publishing hundreds of pages of raw risk assessment data online is unlikely to be effective as the public would be ill-equipped to process, digest or use the information. In comparison, the same data may be more useful for risk assessment 'experts'. In order to measure effectiveness, an examination of the audiences of transparency – who are expected to receive, process, digest and use the information made publicly available – is required. Therefore this thesis evaluates the outcomes of the regulators policies instrumentally by using effective, rather than nominal, measures of transparency.

A subsequent question centres on how *effectiveness* might be measured. Perhaps the most difficult challenge with measuring and evaluating the effectiveness of transparency policies is identifying whether the policy was indeed the cause of a regulatory outcome. This is because there are many confounding variables in real-world settings that are difficult to mitigate in both quantitative and qualitative study designs (King *et al*. 1994; Shapiro, 2002; Coglianese and Bennear, 2005; O'Neill, 2006; Coglianese, 2012). For example, Hood (2006b) makes clear that identifying a causal association between transparency and trust is hard "partly because of 'noise' – everything else that has gone on at the same time (such as generational change, technological change, the spread of education, and particular events such as [regulatory scandals and crises])".

With that said, several authors have argued that effectiveness can still be measured and evaluated usefully. For example, Coglianese (2012) outlines several methods ranging from controlled and randomised experiments to observational studies (quasi-experiments) and qualitative studies (King *et al*. 1994). In the wider transparency literature an increasingly popular approach has been to conduct policy experiments (De Fine Licht, 2014; Löfstedt and Way, 2016a, 2016b; Cucciniello *et al*. 2017). For example, Grimmelikuijsen (2010) examined the effects of transparency on trust experimentally and found that individuals who received more information about government were more negative regarding their perceived competence. Experiments can be particularly useful as they can help to mitigate confounding variables. However, they also suffer from other limitations including, perhaps most notably, serious concerns about a lack of real-world validity. What is needed is an approach that can be used to evaluate the effectiveness of the regulators' transparency policies within its real-world context. In so doing, this thesis provides a case study of the transparency policies initiated by one regulatory authority, the EMA (*see* Chapter IV for a detailed discussion).

(1.3) The European Medicines Agency

The third component of the research question centres on the rationale for choosing the EMA's transparency policies as a case study. The EMA is the decentralized European Union (EU) agency "responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU" (EMA, 2017a). Therefore one of the agency's main responsibilities is to scientifically evaluate applications submitted by pharmaceutical companies seeking authorisation (i.e. a licence) to market (i.e. to sell) a medicine in Europe, which is valid in all EU member states, as well as in the European Economic Area (EEA) countries of Iceland, Liechtenstein and Norway (EMA, 2017a). Pharmaceutical companies are obliged to use the so-called 'centralised procedure' for certain medicines (e.g. for biotechnology products and those treating HIV/AIDS, cancer and diabetes) (*see* EMA, 2017b for a full list). However, for medicines that are not required to go through EMA's centralised procedure, companies can seek approval through a member state regulatory authority such as the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK or the Spanish Agency for Medicines and Healthcare Products (AEMPS) in Spain[3]. In

[3] When applying through member states, pharmaceutical companies can also apply for simultaneous authorisations in more than one EU country through the 'decentralised procedure' or the 'mutual recognition procedure' (*see* EMA, 2017a).

addition, and amongst other activities, EMA is also responsible for safety monitoring (e.g. coordinating the EU's pharmacovigilance system), referrals (e.g. evaluating a safety concern brought up by the Commission or a member state) and inspections (e.g. ensuring compliance with good manufacturing practices) (EMA, 2017a).

Since its inception in 1995, the agency has demonstrated a firm commitment to enhancing transparency (Chapter V) (EMA, 2009; 2014a). In particular, the agency has introduced a diverse array of policies (EMA, 2017c). During the early years, the agency was congratulated for its strong commitment to transparency and communicating proactively with the many actors involved in pharmaceutical regulation (Abbasi and Herxheimer, 1998; Elgie, 2005; Kent, 2005; Gehring and Kraphol, 2007). Notably the introduction of European Public Assessment Reports (EPARs), that seek to provide high-quality information on medicines to healthcare professionals and patients (see EMA, 2017d), was viewed by many as a turning point in the transparency of the traditionally secretive pharmaceutical environment (Lekkerkerker, 2005). Although the agency "inevitably" received increased scrutiny (ISDB, 1998; Abraham and Lewis, 1999; Garattini, 2005; Garattini and Bertele, 2007), transparency was viewed as highly desirable and important for EMA. In turn, the agency went on to introduce many more policies that both met and went beyond its legal obligations (EMA, 2009).

Since 2010, however, the agency has "come under fire" for not being transparent enough (Hampton, 2011). Many organisations and individuals have criticised EMA ranging from medical journal editors and external researchers (e.g. data miners), to campaign groups and opinion leaders, as well as politicians and a succession of European Ombudsmen (Chapter V) (Löfstedt and Bouder, 2014; Bouder *et al*. 2015; Institute of Medicine, 2015; Way *et al*. 2016). In turn, the agency has introduced a "tsunami" of new transparency policies (Löfstedt and Way, 2016a), which its 3rd Executive Director, Guido Rasi, made clear will provide an "unprecedented" level of openness and transparency in EMA and its scientific and non-scientific activities (EMA, 2014a). Most notably, the agency has now provided for the first time public online access to clinical study reports[4] which detail the main scientific data underpinning decision-making in its human medicines committee (EMA, 2014b; Bonini *et al*.

[4] Clinical study reports are documents written by pharmaceutical companies in application for authorisation (i.e. a licence) to market (i.e. sell) a medicine in the EU when applying through the EMA's centralised authorisation procedure. They include detailed scientific and non-scientific data and information on the studies conducted to examine the safety, quality and efficacy of a medicine including clinical overviews, summaries, protocols, documentation and statistical methods.

2014; EMA, 2016a). Specifically, on 20th October 2016 the agency uploaded, for the first time, approximately 260,000 pages of data and information for over 100 clinical study reports relating to (1) a medicine used to treat multiple myeloma (a cancer of the bone marrow) called Kyprolis (carfilzomib), and (2) a medicine used in adults with gout to reduce high levels of uric acid in the blood called Zurampic (lesinurad) (EMA, 2016a). This represents an unprecedented disclosure of data on the studies underpinning scientific regulatory decision-making and something that has not been seen before in the pharmaceutical domain (Rasi, 2016).

Beyond the fact that EMA is a risk regulator that has introduced policies designed to enhance transparency, there are several other reasons why the agency provides an ideal case study for this thesis. First, despite its commitment to the concept EMA has continued to be criticised (Chapter V) (*see* Way *et al*. 2016 for a discussion; Godlee, 2012, AllTrials.net, 2017; Doshi *et al*. 2012; Goldacre, 2012; Willmott, 2013, 2014). Criticisms range from the need to provide more clarity about scientific committee decisions (e.g. on the approval or rejection of a licensing application) (Willmott, 2013, 2014) to strong pressures to publish the actual scientific data that underpins those decisions (e.g. Doshi *et al*. 2012, 2013a). EMA therefore presents a particularly interesting case of an organisation that has seemingly done as much as possible to enhance transparency, yet has found itself coming under intense scrutiny from many actors.

Second, the agency is frequently under the public spotlight. EMA operates in a particularly challenging policy domain or as Groenleer (2009: 141) puts it, they are regulating "such politically sensitive and emotionally-laden issues as pharmaceuticals […], which not only involve enormous economic interests but also concern the public health of millions of EU citizens". Therefore there is much at stake for the public and EMA needs to get its transparency policies right.

Third, the pharmaceutical domain has a complicated multi-level governance structure where transparency and risk regulation have consequences for many actors including industry, non-government organisations, the medical community, healthcare professionals, patient and doctor representative groups, patients themselves and the public (Ghering and Kraphol, 2007; Vos, 2011). Indeed, there are multiple competing interests over the regulation of pharmaceuticals with a variety of different actors. Transparency would therefore very reasonably seem to be

particularly important as is it important that individuals understand the regulators decisions and the reasons for them.

Fourth, examining one agency provides the opportunity to examine different forms of transparency introduced by a single organisation in great depth. Therefore future comparisons of EMA with other organisations can be conducted. Indeed, clarity and sophistication over the different forms of transparency is much needed before multi-organisational comparisons can be made (Chapter II). This can be achieved with a case study approach using multiple methods to examine the EMA (that is, the case study unit) in depth (Chapter IV).

(1.4) Contribution of this thesis

The first main contribution of this thesis is that it provides much needed clarity over the concept of transparency in risk regulation through the creation of a typology. There is significant confusion in the literature and among practitioners (Meijer *et al*. 2015). Debates more often than not end with an agreement that transparency is important but with little discussion about what forms of transparency are needed in the achievement of specific public policy outcomes. Consider the words of EU Commission President, Jean-Claude Junker, when announcing a new set of policies that aim to make EU decision-making "more open and transparent" to the public:

> *"We could do the best possible work but it will be worth nothing if we do not earn the support and trust of the citizens we are working for. So let us be more transparent, because in fact we have nothing to hide. Let us show that this time it really is different and that together we are able to really change and renew Europe.*" (Jean-Claude Junker, 2014).

Although these comments specifically concern the Trans-Atlantic Trade and Investment Partnership free trade agreement negotiations (*see* Lester and Barbee, 2013), they provide a good example of how transparency is often called for (e.g. in official speeches) but with little clarity over what is expected to be made transparent, how, why, and for whom (Gupta and Mason, 2014). This thesis provides a way of disentangling different forms of transparency that are directly connected to varying effects in different contexts. Therefore the typology of transparency in risk regulation offered in this thesis promises to enable researchers and practitioners to debate different forms of transparency with more clarity.

The typology can also be used to bring together the fragmented transparency literature (in risk regulation). The wider literature on transparency has become extensive. Yet, it is seriously fragmented with many different strands focusing on different issues such as governance by disclosure, open government, accountability, democracy, legalism and many others (Florini et al. 1999; Hood and Heald, 2006; Gupta and Mason, 2014). Researchers have also examined the concept from different perspectives and using different methods (O'Connor, 2016). The typology can bring together the multidisciplinary and interdisciplinary literature examining different forms of transparency relating to risk and risk issues. This argument is akin to that of Kasperson *et al*. (1988) who provided a framework that attempted to "overcome the fragmented nature of risk perception and risk communication research by developing an integrative framework capable of accounting for findings from a wide range of studies" (cf. Pidgeon *et al*. 2003; Breakwell, 2007, 2014). To be clear, the transparency typology does not provide a theory of transparency in risk regulation but rather seeks to bring together both theoretical arguments and empirical findings into one organising framework, which can incorporate a range of studies originating from areas as diverse as law, political science, geography, sociology, psychology and beyond.

The second main contribution of this thesis is that it provides much needed empirical research on transparency in risk regulation. Transparency does not always have positive outcomes and can have severe unwanted effects (Hood, 2001; Hood and Heald, 2006; Meijer *et al*. 2015). Moreover, recent findings reveal that transparency can be well suited at addressing some issues and poorly suited at addressing others (Cucciniello *et al*. 2017). What is needed is an understanding of when transparency is effective and when it is not and why. However, there has been a dearth of empirical work examining the effects of transparency under various conditions, and in what contexts different policies can be effective or not (Etzioni, 2010; Cucciniello *et al*. 2017). Most studies have been theoretical or anecdotal. The majority of studies that have provided empirical evidence have also been experimental in their design (e.g. Grimmelikhuijsen *et al*. 2010; De Fine Licht *et al*. 2014). Therefore providing a real-world empirical examination of the transparency policies initiated by one regulatory agency can significantly contribute to the empirical literature on transparency in risk regulation. In addition, the thesis has the potential to be used for comparisons with future analyses of transparency in risk regulation whether that is in comparing different countries and jurisdictions, policy domains or both.

The third main contribution of this thesis is that it can provide concrete recommendations for EMA and its transparency strategy. The agency has not conducted a systematic review of its transparency policies (Löfstedt, 2013). It is also coming under greater pressure both on its approach to transparency and how it has been using its resources to enhance transparency (Way *et al*. 2016). Therefore this thesis provides an in-depth analysis of EMA that can help to inform the regulators' transparency strategy. This is particularly important as there is a need for EMA to become more sophisticated with its approach to transparency and, as discussed in the previous section, its policies affect the lives of millions of EU citizens many of whom have long-term disabling medical conditions.

(1.5) Thesis organisation

The thesis is organised as follows. A typology of transparency in risk regulation is first offered (Chapter II). The typology sets forth a clear distinction between various transparency policies introduced in risk regulation. This includes what type of policies the regulators are making transparent (i.e. objects), how (i.e. mechanisms), why (i.e. goals/reasons), and for whom (i.e. audiences). Creating these clear distinctions leads on to a structured review of the burgeoning but seriously fragmented literature relating to transparency in risk regulation (Chapter III). This centres on the arguments for and against different forms of transparency in risk regulation focusing on policy domains and regulatory contexts related to health, the environment, and safety.

The research methodology is then presented (Chapter IV). The chapter first elaborates on how the effectiveness of EMA's transparency policies are measured and evaluated in this thesis. This includes an understanding that the perspectives of multiple competing actors is required. It also sets out the rationale for choosing an in-depth case study.

The subsequent three chapters present the results and analysis of the EMA case study. First, a historical analysis examines how the agency's transparency policies evolved over time spanning from its inception in 1995 to December 2016 (Chapter V). A background on the creation of EMA is detailed, which focuses on how concerns about transparency were present even before the agency was established. Three subsequent and distinct phases in the development of EMA's transparency policies are then identified and discussed in turn. This

includes the early years (1995-2000), a period of consolidation (2000-2010), and what is described in this thesis as "the New Pharmaceutical Transparency Era" (2010-). Amongst other findings, the analysis shows that EMA's approach to transparency and the type of policies it has initiated has changed significantly since its inception. Most notably, since 2010 EMA has focused much of its resources and attention on the data and information that underpins decision-making in its scientific committees and, especially, clinical trial and suspected adverse reaction data. The historical analysis leads on to and provides the foundations for an in-depth examination of EMA's five main informational input transparency policies (Chapter VI). These centre on three clinical trial data transparency policies and one policy on uploading suspected adverse drug reaction data online. The results and analysis of the patients' and medical doctors' surveys are then presented (Chapter VII).

In the penultimate chapter, an evaluation of the effectiveness of EMA's transparency policies is provided by discussing the EMA case study results (Chapter VIII). The chapter specifically addresses the research question. Broadly speaking, the chapter explains that EMA's transparency policies have both positive and negative outcomes and in order to answer the debate about effectiveness an understanding of whose perspective counts is central in the multi-actor pharmaceutical environment.

Finally, the thesis concludes by explaining how the research has contributed to the broader literature (Chapter XI). It also provides four recommendations that centre on what should be done next.

Chapter II: DEVELOPING A TRANSPARENCY TYPOLOGY

This chapter presents an original typology of transparency in risk regulation. Several authors have offered organising typologies and frameworks that seek to disentangle the fragmented transparency literature (Lodge, 2004; Prat, 2006; Heald, 2006a; Coglianese, 2009; Mitchell, 2011; De Fine Lincht *et al*. 2014; Gupta and Mason, 2014; Meijer *et al*. 2015). This includes a transparency toolbox (Lodge, 2004) and government transparency assessment framework (Meijer *et al*. 2015), as well as multiple other distinctions between different forms of the concept (e.g. reasoned versus process transparency[5]) (Hood, 2007; De Fine Licht *et al*. 2014). Although these approaches have provided much needed sophistication, none of them can be directly applied to risk regulation (at least for the purposes of this thesis). This section therefore provides an original typology that will form the foundations of this chapter and thesis. In particular, the typology makes important distinctions between different forms of transparency in risk regulation. This includes clear distinctions between various policy objects (what is being made transparent?), mechanisms (how are those objects being made transparent?), aims/reasons (why are the regulators making them more transparent?), and audiences (for whom are the regulators making these objects more transparent?).

(2.1) The need to develop a typology

The literature on transparency in risk regulation is seriously fragmented. The concept figures in a quite remarkable array of published texts and disciplines including law, architecture, democracy, national defence, surveillance, regulation, public administration and others (Florini, 1999; Fisher, 2010; Meijer *et al*, 2015; Cucciniello *et al*. 2017). One of the reasons why the literature is so fragmented is that transparency is an ambiguous concept (section 1.1). In risk regulation alone, different transparency policies have sought to make many regulatory processes more transparent and in different ways. For example, EMA has introduced policies that seek to enhance the transparency of the data that underpins its regulatory decision-making by publishing clinical study reports online (section 1.3) (EMA, 2014a, 2014b, 2016a). In contrast, EFSA, the decentralised EU agency responsible for food safety, has introduced another quite different policy that seeks to enhance the transparency of its managerial decision-making process by web-streaming all board meetings (Vos, 2009). Although both authorities

[5] For an explanation of reasoned versus process transparency *see* De Fine Licht *et al*. (2014).

have sought to enhance transparency, these two policies clearly provide very different forms of transparency.

Transparency policies have also been advocated by different actors – such as by regulators, non-governmental organisations (NGOs), industry, and other influencers – for often rather different reasons and in different contexts. For example, the US Toxics Release Inventory seeks to induce targeted actors (e.g. industry) to adopt less risky behaviour (*see* Kraft *et al*. 2011). The TRI database has been advocated as a novel policy tool and a form of 'soft' governance by its advocates (Fung *et al*. 2007; Kraft *et al*. 2011) or what Mitchell (2011) categorises as "Transparency FOR governance" [emphasis in original]. In contrast, one of EFSA's most recent policies has provided public access to "a treasure trove" of food safety data, which ultimately seeks to improve the evidence base for regulatory decision-making, increase public scrutiny of regulation and enable the re-use of data for other purposes or what Mitchell (2011) categorises as "Transparency OF governance" [emphasis in original]. Again, these two examples clearly provide very different forms of transparency, which seek to achieve very different goals, for very different audiences, and in different regulatory contexts.

(2.2) Transparency objects

What do risk regulators seek to make more transparent? At least three *objects* of transparency in risk regulation can be identified (Figure 2.1)[6] (Heald, 2003: 729, 2006: 30), namely:

- Informational *inputs*
- Transformative *processes* (including procedural and operational components)
- Policy *outputs*

These three objects are the specific scientific and non-scientific regulatory events and processes that risk regulators choose or may be required to make more visible to outsiders (ibid, 2006).

[6] In Heald's (2003, 2006) original analytical framework two additional objects of 'linkage processes' and 'outcomes' are included as well.

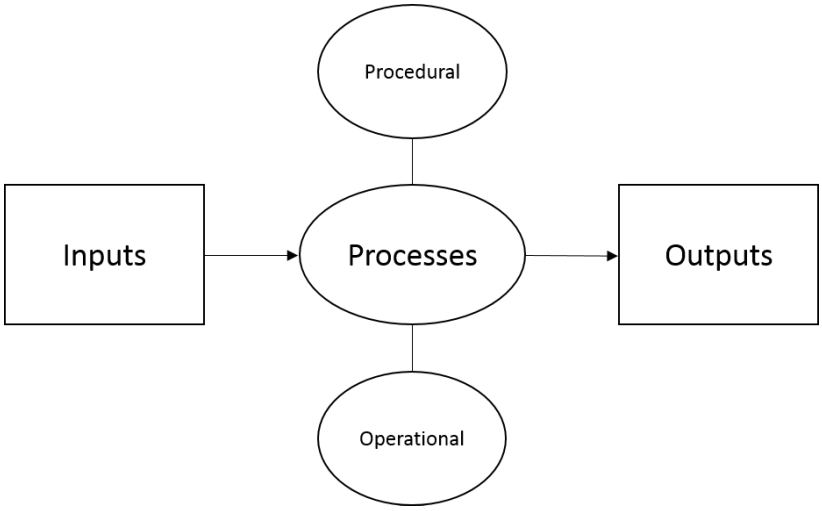

Figure 2.1: Diagram showing three objects of transparency that risk regulators might seek to make more visible. Adapted from Heald (2006a: 30).

Informational inputs are the first transparency object (Figure 2.1). They include all the data and information that is gathered and used by risk regulators to inform the decision-making process. Therefore inputs are the main scientific and non-scientific evidence that underpins decision-making (e.g. in a scientific committee). Regulators might seek to make, for example, open comment periods, licensing applications, raw scientific data, academic journal articles, or other relevant information more transparent. Examples include clinical study reports (e.g. in pharmaceuticals), food risk assessment data (e.g. in food safety), hospital mortality rates (e.g. in patient safety), crime statistics (e.g. in policing), industrial pollution emission data (e.g. in environmental protection), surgical performance results (e.g. in healthcare), automobile rollover accident data (e.g. in health and safety), and so on (Fung *et al*. 2007). For example, while pharmaceutical regulators – such as EMA, FDA or Health Canada – require clinical trial data in order to approve or reject a licensing application, health and safety regulators – such as the UK Health and Safety Executive or the US Occupational Safety and Health Administration – require incident data (e.g. accident and sickness absence rates) to identify and monitor workplace hazards.

Going further, regulatory organisations may be required to obtain further input information that they may not have in their possession. For example, Article 5 of the 1998 Aarhus Convention[7] on environmental information disclosure includes far-reaching obligations for regulators (and

[7] The Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters.

other public authorities) including the requirement that, in some cases, they are legally obliged to *collect* and then disseminate environmental information (*see* Mason, 2014a: 89).

Transformative processes are the second transparency object (Figure 2.1) (*see* Heald, 2006a: 31-32). They are the means by which inputs are transformed into outputs and can be sub-divided into procedural and operational components (Heald, 2003: 729). The *procedural* component of transformative processes "relates to the rules, regulations and procedures adopted by an organization" such as the rules on what decisions can be made and how (ibid, 2006: 31). Regulators may want to make transparent, for example, the organisation's standard operating procedures, work instructions, guidelines, or the rules relating to conflicts of interest. Procedural process objects can collectively be understood as transparency about the 'rule book' (ibid, 2006: 31) or "the rules to be followed" (Lodge, 2004: 128). Lodge (2004) goes further and makes clear that this rule book will also have been created through its own separate decision-making process (i.e. the decision-making process for setting rules and standards). This process can in itself be sub-divided into the three transparency objects described in this section: inputs (e.g. the evidence for making a new rule), processes (e.g. deliberations about a proposed new rule), and outputs (e.g. the actual rule and guidance documents) (Figure 2.1). In comparison, the *operational* component of transformative processes refers to "the application of these rule books to particular cases" (Heald, 2006a: 32). This can be best understood as how the rules are interpreted and applied to making a decision. For example, the regulators might want to make the actual discussions taking place between decision-makers, such as scientific committee discussions, more transparent.

Decision-making outputs are the third transparency object (Figure 2.1). This most commonly refers to the actual decisions or policies made during the decision-making process as well as the reasons for them. For example, an expert pharmaceutical committee might refuse or approve a new medicine (e.g. after reviewing a licensing application from a pharmaceutical company) while a chemical safety committee might recommend a chemical to be banned (e.g. after conducting a risk assessment). The regulators may want to make their decisions as well as their reasons for making those decisions transparent. For example, the Dutch Gezondheidsraad, an independent Dutch advisory body charged with providing government with scientific advice on matters of public health, often produces a report or summary of its opinions and may go on to explain the rationale for its conclusions (e.g. in a public speech)

(Bijker *et al*. 2009). Indeed, there are many outputs from the decision-making process that can be made more transparent that are directly relevant to the decision made and context. This might include communicating a safety alert, providing recommendations, updating guidance documents, or providing new benefit/risk information.

(2.3) Transparency mechanisms

How have risk regulators sought to make different objects more transparent? The second distinction that needs to be made are the policy *mechanisms* or means for making different objects more transparent. Since the late 20th century, the main mechanisms for enhancing transparency have predominately involved regulators providing more information online in what has been described as 'internet-mediated' transparency (Meijer, 2013), 'computer-mediated' transparency (Meijer, 2009) or 'e-government' (Wong and Welch, 2004). That is not to say that all mechanisms have been limited to the Internet. Examples of offline mechanisms might include receiving paper-hand-outs during a public meeting that are unavailable online (Meijer *et al*. 2012) or allowing physical public access to an archive or repository (Hetherington, 2011). With that said, this thesis focuses on computerised or 'internet-mediated' transparency mechanisms.

Mechanisms for enhancing decision-making transparency can be coupled with the three objects of transparency already identified (i.e. inputs, processes and outputs). First, input mechanisms have primarily involved uploading information used to inform the decision-making process online such as the actual comments from public consultations or reports on the scientific studies used to inform the regulatory process. Second, transformative process mechanisms seek to make either procedural or operational components more transparent. While some mechanisms involve simply uploading data and information online (e.g. standard operating procedures, committee guidelines etc.), others require that the regulators collect the information before being able to do so (e.g. taking meeting minutes before uploading them online) (Piotrowski and Borry, 2010). Further still, more radical operational process mechanisms include providing audio or video recordings and even web-streaming meetings live (EFSA, 2002; Piotrowski and Borry, 2010). Third, output mechanisms are designed to make decision-making outputs more transparent. This might involve an expert providing an *ex-post* explanation in layman's language of a decision taken (e.g. in a press conference), posting a question and answer sheet

online explaining the rationale for a decision taken or publishing a scientific advisory committee report online (Woloshin and Schwartz, 2002; Issing, 2005; Bijker *et al*. 2009: 117-124). Improving how decisions and the reasons for them are communicated with outsiders has traditionally been a major occupation of risk perception and communication research (Slovic, 2000; Kahneman, 2011; Fischhoff *et al*. 1995, 2011).

Several further broad distinctions between different transparency mechanisms can be made. First, mechanisms can be formal or informal. While a formal mechanism for enhancing transparency might include publishing meeting minutes online, an informal type might include information that is 'leaked' or a lobbyist learning about policy details at a wine bar (Meijer *et al*., 2012). Transparency does not have to be a deliberate or conscious action of an organisation. Second, a clear distinction can be made between real-time transparency, "information that is released as soon as it is created" (e.g. live web-streams of meetings), and retrospective transparency, "information available only after embargoes or time delays" (e.g. publishing meeting minutes online later) (Heald, 2006a). Timeliness is an important transparency policy consideration such as for enabling *meaningful* participation and making policy information available before a regulatory decision has been made (Grimmelikhuijsen and Meijer, 2012; Coglianese, 2012). Third, a broad distinction can be made between proactive and reactive transparency policies. While proactive policies often involve uploading information online (e.g. posting all input information onto a web-portal), reactive policies might include responding to requests for information such as with Freedom of Information (FOI) requests (Birkinshaw, 2006; EMA, 2010a). For Fox (2007: 665), this represents an important distinction between proactive versus demand-driven dissemination.

(2.4) Transparency goals

Why have regulators sought to enhance transparency? Many instrumental arguments for enhancing transparency have been provided in different regulatory contexts (Chapter I). Some have argued that transparency can curb corruption and stimulate more efficient and effective decision-making by contributing to 'good governance' (Hood and Heald, 2006). Other arguments range from its apparent ability to strengthen the information position of citizens and enable (meaningful) public participation in decision-making (Stiglitz, 1999) to arguments over improving the overall quality of risk regulation and reducing conflicts of interest (Carpenter

and Moss, 2013), as well as inducing industry to reduce risks to public health and the environment (Fung *et al*. 2007; Weil *et al.* 2013) and building public trust in risk regulation. Indeed, a multiplicity of transparency goals have been put forward in different (regulatory) contexts.

Although many of these transparency goals have been discussed, at least three overriding ones outlined here have taken prominence in risk regulation. First, transparency seeks to *enable greater participation*. Arguments have primarily centred on the idea that transparency can reduce information asymmetries between decision-makers and the public and that this is an essential pre-requisite for meaningful public participation in government decision-making (Stiglitz, 1999; Michener and Bersch, 2016). Second, transparency seeks to enable outsiders to *re-use scientific data* and other decision-making information. Some of the main arguments have been that outsiders can use this information in order to, for instance, double check the regulators' decisions or (re)use it for other purposes (e.g. conducting follow-up studies or open data programmes). Third, transparency seeks to *(re)build trust* in institutions and confidence in decision-makers. Although often loosely connected, many risk regulators expect they will be viewed as open and honest as they will not be hiding any information. This is understood to, in turn, build public trust.

(2.5) Transparency audiences

Who are regulatory transparency policies intended for? Transparency policies have various *audiences* and it is important to clarify who is revealing what information to whom (Gupta and Mason, 2014: 25). The direction of transparency discussed in this chapter is *inwards*, whereby "outsiders can observe what is going on inside [a regulatory] organisation" (Heald, 2006a)[8]. Frequently these 'outsiders' are left implicit such as in official speeches where a policymaker might note that information is being made 'publicly available' but with little clarity over which actors are being referred to (Chapter I). In risk regulation, outsiders vary widely and might include the public, other regulatory bodies, external researchers, industry, scientific journal editors, the media, non-governmental organisations, and many others (as well as any

[8] Other directions of transparency can also be distinguished between including upwards, downwards and outwards forms (see Heald, 2006a: 27-28 for a discussion). For example, outwards transparency might be associated with government surveillance of the public such as in relation to the British Government Communication Headquarters' (GCHQ) attempts to monitor public internet usage (e.g. regarding terrorism handbook downloads) (*see* e.g. Brin, 1998; Andrew, 2009).

combination of these simultaneously). Indeed, different risk-related policy domains have further labels that can distinguish between other targets of transparency policies such as farmers, healthcare professionals (e.g. nurses, doctors or pharmacists), toxicologists, patients, and so on.

The different audiences of the regulators' transparency policies are, however, often poorly articulated and loosely connected to different goals. For example, although releasing thousands of pages of safety-related information may be useful for expert outsiders wishing to re-analyse or re-use information to check-up on the regulators' decisions, it is clearly less useful, and could perhaps even be confusing, to non-expert members of the general public. In contrast, while providing an *ex-post* explanation of a decision-taken (i.e. output mechanism) may be more helpful to a lay member of the general public (e.g. in understanding how and why a regulatory decision was made), the same policy would be less helpful for an external researcher that wants to re-analyse/re-use scientific data used to inform the decision-making process. For this example specifically, a further distinction can therefore be made between *indirect* and *direct* transparency (Hood, 2007). While indirect transparency can be defined as information that can only be verified by technical experts (e.g. complex raw data), direct transparency can be classified as information that is visible to or verifiable by the public at large (e.g. well communicated safety information) (Hood, 2007). Both types imply very different audiences of transparency.

Chapter III: TRANSPARENCY IN RISK REGULATION

> *"There is no easily identified community of transparency scholars, nor is there agreement on appropriate methods or theoretical constructs"*. (Robert O'Connor, US National Science Foundation, 2016)

This chapter utilises the typology developed in Chapter II in order to review the literature on transparency in risk regulation. First, an overview of the most widely discussed mechanisms for making regulatory processes and events (i.e. outputs, processes and inputs) more transparent is provided. This discussion particularly emphasises how transparency in risk regulation can be directly linked to the evolution of risk communication research and practice since at least the mid-1980s. Second, a more in-depth discussion relating to decision-making 'input' policies is provided. This is primarily because these types of transparency policies have become increasingly popular (and controversial) in European risk regulation since 2010 (including at the EMA) (*see* Way and Löfstedt, forthcoming; EMA 2014a, 2014b). Therefore input policies will become the main focus of the empirical chapters of this thesis (*see* Chapter IV for a discussion). The review of input transparency policies examines three main perspectives taken in the literature, namely: (1) soft risk regulation; (2) scrutinising regulatory data; and (3) data quantity and quality. Third, the literature examining the goal of building public trust, that is relevant to all mechanisms and objects, is reviewed. Although there are many overriding goals of transparency, this specific goal is reviewed because the majority of risk regulators argue that building public trust in risk regulation is the ultimate goal of enhancing transparency.

(3.1) Debating transparency policies

Over the past 30 years risk regulators have introduced many new policies that seek to make different decision-making events and processes more transparent. At the same time an extensive academic literature has emerged on the topic of transparency that *includes* debates over the arguments for and against different mechanisms – such as publishing regulatory data or uploading scientific committee meeting minutes online – that are designed to make different objects (i.e. outputs, processes, or inputs) more transparent. This section provides an overview of this fragmented literature organised into three sub-sections: output mechanisms (3.1.1), process mechanisms (3.1.2), and input mechanisms (3.1.3).

(3.1.1) Output mechanisms

One of the overriding reasons for making outputs more transparent is so outsiders can understand what decisions the regulators (and other bodies) have made, how they came to their decisions and why[9]. One main mechanism for doing so is to create a (scientific) report. As Bijker *et al*. (2009: 107) put it, "the ideal is, of course, that [the decision-making process] yields advice of such high quality that the evidence and arguments in the reports will do all the persuasive work by themselves and will convince policy makers, professionals, and the public that the advice should be followed". In turn, outsiders can take appropriate action based on the ideal of evidence-based decision-making. However, a large literature has shown that simply creating and sharing well-written reports is rarely sufficient for achieving output transparency (Bijker *et al*. 2009; Arvai and Rivers III, 2014). This is especially true when decisions concern risk and risk issues relating to public health and the environment which can affect many actors and the lives of millions of people (Renn *et al.* 2011).

Moreover, debates over output transparency mechanisms can be directly linked to the sub-field of risk communication (Arvai and Rivers III, 2014), which, for Fischhoff (2009: 940), "examines the processes that determine how communication with lay people [and external experts] enhances or degrades their decision-making ability". To be clear, output transparency requires that outsiders can receive, digest, process and use the information made available by the regulators and so it needs to be 'communicated' (section 1.1). Since at least the late 1970s, this sub-field has evolved significantly with researchers and practitioners gaining a greater understanding about the complexities of communicating risk information effectively (e.g. the outcomes of decision-making). Several comprehensive literature reviews have detailed the evolution of risk communication relating to, for example, the environment/technology (Kasperson and Stallen, 1991; Boholm, 1998; Fischhoff, 1995; Leiss, 1996; Löfstedt and Frewer, 1998; Slovic, 2000; Frewer, 2004; McComas, 2006), food safety (Löfstedt, 2006; Wardman, 2008; Frewer *et al*. 2014), pharmaceuticals (Bennett *et al*. 2010; Fischhoff *et al*. 2011; Chakraborty and Bouder, 2013; Way *et al*. 2017) and others (e.g. Boholm, 2015). The intention here is not to 're-invent the wheel' by re-fashioning these already comprehensive

[9] To be clear, this is regardless of whether the decision-making process itself was fully open and participatory or not.

literature reviews. Rather, some of the major milestones and conceptual avenues in risk communication theory and practice can be linked to the concept of output transparency.

Early risk communication mechanisms – that dominated in the 1970s and early 1980s – sought to persuade outsiders to accept the outputs of regulatory decision-making (Kasperson and Stallen, 1991; Fischhoff, 1995; Leiss, 1996). Risk communication was viewed as the last stage of risk management after the expert risk assessment process and selection of risk management options had been completed (Jardine and Driedger, 2014: 258). Risk communicators primarily took a technocratic top-down approach to communicating outputs, which aimed to "teach the public about 'real' risk so they can act 'rationally' and make informed decisions about what risks to take or not to take" (Boholm, 2008). Often described as the "deficit model" (Hilgartner, 1990), the ultimate goal was to 'rectify' the gap and align perspectives between the 'lay' public and risk assessors (and other scientists) in order to bring the public's risk perceptions in line with 'expert' assessments (Woolgar, 1996; Frewer, 2004; National Academy of Sciences, 2016: 2-9). Output transparency has therefore traditionally been confined to a one-way model of conveying knowledge and informing the public about decisions made by 'expert' decision-makers (National Academy of Sciences, 2016).

Over the past 50 years, risk communication research and practice has evolved significantly (Fischhoff *et al*. 2011; Fischhoff, 2013; Canadian Academy of Sciences, 2015; National Academy of Sciences, 2016). One of the most notable milestones was the US National Research Council's (NRC) publication, titled '*Improving Risk Communication*' (NRC, 1989). The book represents a paradigm shift in risk communication because, as Jardine and Driedger (2014: 258) comment, "risk practitioners began to reframe the issue of risk communication as an application of communication theory and practice rather than simply an extension of risk assessments". For example, in a seminal paper (Fischhoff, 1995) identified eight important – but empirically unsubstantiated (Breakwell, 2007) – developmental stages in the practice of risk communication. Among many other arguments, the article emphasises that conveying factual knowledge alone – such as by writing a well-written scientific report – is unlikely to be sufficient for achieving the regulators' risk communication goals (Brewer, 2011; Fischhoff *et al*. 2011, 2013; National Academy of Sciences, 2016).

The sub-field of risk communication has since explored many new conceptual angles (McComas, 2006; Boholm, 2015). These range from arguments over the need to build public trust in risk regulators and assessments (Wynne, 1980, Siegrist and Cvetkovich, 2000; Poortinga and Pidgeon, 2003; Löfstedt, 2005; Siegrist *et al*. 2007; Earle, 2010) to recognizing the importance of the social amplification and attenuation of risk (Kasperson *et al*. 1988; Renn, 1991; Pidgeon *et al*. 2003; Breakwell, 2007, 2014) and promoting public participation and deliberation (Petts and Brooks 2006; Pidgeon and Rogers-Hayden, 2007; Wesselink *et al*., 2011). Amongst many other findings, the risk communication literature has also debated numerous mechanisms for communicating about risk and risk issues that have varying advantages and disadvantages in different contexts[10] (Slovic, 2000; Arvai and Rivers III, 2014; Fischhoff *et al*. 2011, 2013; Boholm, 2015). This includes arguments for and against mechanisms ranging from written information (e.g. press statements, information leaflets and committee reports) (Morgan *et al*. 2002; Fleishman-Mayer and Bruine de Bruine, 2014; Way *et al*. 2017) to infographics (Spigelhalter *et al*. 2011), visual and audio tools (Downs, 2014) and social media more generally (Moorhead *et al*. 2013; Brossard, 2013; Neeley, 2014). Therefore output transparency can be directly linked to this now extensive literature.

(3.1.2) Process mechanisms

The concept of process transparency can also be directly linked to risk communication research and practice. A major area of academic and policy interest has centred on the importance of public participation and deliberation in the decision-making process (Petts and Brooks 2006; Pidgeon and Rogers-Hayden, 2007; Wesselink *et al*. 2011; Löfstedt, 2005; Löfstedt *et al*. 2012). Up until the late 1970s European risk regulation was dominated by a 'consensual' approach to decision-making that focused on negotiated and paternalistic systems (Kelman 1981; Brickman *et al*. 1985; Vogel 1986, 2012; O'Riordan & Wynne 1987; Moran, 2003). This meant that there was little process transparency (at least in Europe). As Marquand (1988: 178 In: Moran, 2003) explains with regard to 1970s Britain:

> *"The atmosphere of British government was that of a club, whose members trusted each other to observe the spirit of the club rules; the notion that the principles underlying the rules should be clearly defined and publicly proclaimed was profoundly alien."*

[10] These are rarely described in risk communication research and practice as 'output transparency mechanisms'. A more common label would be, for example, risk communication 'tools' (EMA, 2014; EFSA, 2016; Way *et al*. 2017).

The consensual approach notably emphasised a cosy and friendly relationship between the regulators and regulated and was characterised by closed-door meetings with elite representatives (Moran, 2003). As Jasanoff (1993 In: Vogel, 2001: 2) put it: "policy decisions about risk remained (closed to the public) … the preserve of experienced bureaucrats and their established advisory networks". Although the European system was considered effective at the time (Vogel, 1986; Löfstedt, 2004)[11], it has since become antiquated with some going as far as saying it is "no longer viable" (Majone and Everson, 2001: 129), "obsolete" (Leiss, 2000) or even "dead" (Pollitt and Bouckaert, 2011; Bartle and Vass, 2007; Löfstedt *et al*. 2009). For Löfstedt (2004), in place of consensual decision-making a new "participatory-transparent model" of regulatory decision-making emerged that, amongst other changes[12], places a greater emphasis on participation and deliberation in European regulatory decision-making (also *see* Löfstedt *et al.* 2011; Löfstedt, 2004; Löfstedt *et al*., 2009; Rothstein *et al.* 2013; Meijer *et al*., 2013).

In this context, one central argument has been that process transparency is essential for meaningful participation and effective risk communication (Frewer, 2004). Perhaps Paul Slovic, writing in 2000, put it best:

> *"The limitations of risk science, the importance and difficulty of maintaining trust and the subjective and contextual nature of risk point to the need of a new approach – one that focuses on introducing more public participation into both risk assessment and risk decision-making to make the decision process more democratic, to improve the relevance and quality of technical analysis, and increase the legitimacy and public acceptance of the resulting decisions"* (Slovic, 2000).

Two documents provide key milestones in this trend towards promoting public participation and enhancing process transparency (*see* National Research Council, 1996 and US Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). As Jardine and Driedger (2014) explain, these documents "represent a fundamental change from a focus on communication *effects* to a recognition that communication is a *process* that is

[11] For example, Vogel, writing in 1986, comments: "Britain's emphasis on voluntary compliance has not proved any more- or less- effective in achieving its objectives than the more adversarial and legislative approach adopted by policymakers in the United States".

[12] One large strand of the literature has also sought to understand the drivers and reasons for this shift (e.g. Pollit and Bouchaert, 2011; Vogel, 2014; Weiner *et al*. 2014), although this is beyond the scope of this review chapter (also *see* Hood, 2006b; Ruijer and Meijer, 2016).

inextricably linked to the analysis and deliberation of the risk area being communicated" [italics in original] (Jardine and Driedger, 2014). In turn, a new model of risk communication developed that centred on consensus building and conflict resolution (Renn, 2008; Fischhoff, 1995; Leiss, 1996; Petts and Brooks, 2006). In other words, researchers and practitioners began to recognise the need to "integrate communication and consultation throughout the risk management process so that public values can inform and influence the shaping of risk management strategies" (Jardine and Driedger, 2014).

In seeking to enhance procedural and operational process transparency, several main mechanisms have since been introduced by risk regulators. The first set of mechanisms centres on the online publication of numerous procedural process documents such as those relating to expert representative guidelines and standard operating procedures. Although many regulatory bodies have disclosed such documents, only very few authors have debated the arguments for and against doing so (Piotrowski and Borry, 2010; Lowenstein *et al*. 2011; Cain *et al*. 2011). With that said, one main argument is that publishing procedural documents online is essential for enabling public participation and accepting regulatory decisions (Grimmelikhuijsen, 2010; De Fine Lincht *et al*. 2014). If the public knows the limits of what decisions the regulators can make then they may be more willing to accept those decisions and the legitimacy of the process (Grimmelikhuijsen, 2010; De Fine Lincht *et al*. 2014). On the other hand, a few authors have also criticised specific mechanisms. In particular, Lowenstein *et al*. (2011) explored various psychological factors that can complicate the disclosure of scientific committee conflict of interest statements. For example, one issue is that when committee experts disclose potential conflicts of interest they can be subject to *strategic exaggeration,* "the tendency of advisors to inflate the bias in their advice to counteract any discounting that may occur due to disclosure" (Lowenstein *et al*. 2011: 423).

In contrast to *procedural* transparency, the lion's share of the literature has focused on *operational* process mechanisms (Hilgartner, 2000; Bijker *et al*. 2009; Vos, 2009). One particularly popular mechanism has been to upload the minutes of meetings online. Well-written and clear meeting minutes can be easily digestible and readily understandable for outsiders. However, two main limitations of meeting minutes are that they can be uploaded too late in the decision-making process to enable meaningful participation (i.e. decisions have already been made) and important policy details may have been intentionally or unintentionally

omitted. For example, Yin (2009: 103) comments that the "verbatim" transcripts of official US Congress hearings have been deliberately edited – by the congressional staff and others who may have testified – before being printed in final form".

A second more radical mechanism is to web-stream meetings live. This can provide outsiders with an instantaneous and complete visual and audio insight into meetings. Examples include EFSA's decision to web-stream all board meetings in 2002 (Vos, 2009) or the 1989 introduction of television cameras in the UK House of Commons, the latter of which sought to engender greater public respect for the work of MPs and encourage greater public participation in government (Coleman, 2004). One main advantage is that outsiders do not have to attend meetings in person. For example, the Norwegian Association of Local and Regional Authorities stated in 2005 that "all municipalities should implement webcasting of local council meetings by the end of 2009" so that the public can observe local council meetings "independent of time and distance" (Berntzen, 2013). Therefore there are important policy considerations for introducing different mechanisms for enhancing operational process transparency.

There are also arguments that encompass both procedural and operational processes. These include the promised ability to enable outsiders to monitor the powers of the regulators and build public trust in risk regulation (*see* Meijer *et al*. 2015). However, at least two main arguments have been particularly prominent in the literature (Frewer, 2003; Wynne, 1989; Fironio, 1990; Wardman, 2008). The first is that process transparency is expected to strengthen the information position of citizens so that all actors can meaningfully contribute to the risk management process (Bovens *et al*. 2008; Piotrowski and Borry, 2010). This is strongly linked to a large literature on building a strong democracy (Meijer *et al*. 2015) as well as arguments that leaving risk assessment and management to 'scientific experts' is ineffective and too technocratic (Wynne, 1989; Bijker *et al*. 2009; Vos, 2012). Therefore many scholars argue that process transparency is an essential pre-requisite for *meaningful* participation as information asymmetries between the regulators and regulated can be reduced (Stiglitz, 1999; Meijer *et al*. 2012; Michener and Bersch, 2016).

The second main argument is that process transparency can help outsiders better understand risk regulation including the difficulties of and limits to decision-making. This incorporates

arguments relating to improving procedural fairness and acceptance, increasing public control of decision-making and, as De Fine Licht *et al*. (2014: 114-115) put it:

> *"… [process transparency and deliberation can] both inform the citizens of the facts in the case and clarify—and possibly increase the tolerance for—different normative values and worldviews defended by representatives of different groups and perspectives that feed into the decision".*

In turn, this is expected to raise the public's willingness to accept regulatory decisions (De Fine Licht *et al*. 2014: 115). Those outside the regulatory process are expected to 'see' the workings of regulatory agencies such as how responsibilities are divided amongst different groups (e.g. industry and regulators) (Grimmelikhuijsen, 2010:117). The public can gain a clear understanding of how many risk issues are highly complicated and require difficult trade-offs to be made. For example, some have argued that enhancing process transparency can help to explain the inherent uncertainties in risk-related decision-making (Beck *et al*. 2015; Institute of Medicine, 2016; National Academy of Sciences, 2016).

However, although there are persuasive arguments, other researchers have provided counter-arguments (Vos, 2009; Bijker *et al*. 2009; Hilgartner, 2000). One is that process transparency can reveal to outsiders that they lack real influence in the decision-making process leading to frustration or as Ulbig (2008 In: De Fine Licht, 2014: 116) puts it: "voice with little influence produces more negative reactions than no voice". One particularly noteworthy conceptual approach has centred on Erving Goffman's (1959) concept of 'dramaturgy', the study of how meaning is generated in drama and performance (Kennedy, 2010), which draws on the metaphor of a theatre to explain human behaviour (*see* Hilgartner, 2000 for a discussion). By deploying this concept, a growing number of scholars have made an important distinction between 'frontstage' and 'backstage' decision-making (Hilgartner, 2000; Bijker *et al*. 2009; Vos, 2009). The main argument is that, similar to a theatre setting, maintaining some level of 'backstage activity' is essential to the effective workings of scientific committees for at least three main reasons.

The first reason is that conducting all decision-making activity in public can result in scientists and other experts being pressurised by interest groups (e.g. political and interest lobby groups) (Bal *et al*. 2004). In turn, this can result in paralysing the regulatory process. Decision-makers

can be left exposed if they are unable to discuss certain sensitive and complicated issues in private or as Vos (2009: 257) puts it:

> *"…allowing access to meetings of scientific bodies is considered by some authors to be particularly troublesome, as this could lead to the political pressuring of scientists and hence to a further politicisation of science, risking paralysis of the process".*

This is not a hypothetical scenario and has happened before such as with scientists in the Scientific Veterinary Committee during the BSE crisis (Vos, 2009: 258). Therefore there are strong arguments for why maintaining some level of 'backstage' activity is important for the effective functioning of scientific committees.

A second closely connected argument is that keeping scientific discussions backstage can enable participants to feel free to discuss issues openly and hence produce high quality opinions through debate. A seminal book by Bijker *et al*. (2009) found that many discussions at the Dutch Gezondheidsraad needed to be non-transparent in order to resolve differences in opinion between the various actors involved in decision-making (Löfstedt and Bouder, 2014). For Coglianese (2009), this might be described as 'fishbowl' transparency where every move and decision made by decision-makers is scrutinised. Thus some authors have argued that some aspects of process transparency – or full 'fishbowl' transparency – should be limited so that scientists can exchange opinions backstage but also incorporate the views of other important actors onstage (Löfstedt and Bouder, 2014).

A third main argument has been that enhancing process transparency may actually erode rather than build public trust (*see* section 2.3.4 for further discussion). In particular, some authors have expressed concerns that outsiders and especially the public will become disenchanted with how regulators seemingly "muddle through and bicker throughout the decision-making process" (Löfstedt and Bouder, 2014: 77; also *see* Lindbloom, 1959). For example, a growing body of research has shown that communicating uncertainties in risk regulation is complicated and challenging and can ultimately, if handled poorly, result in eroding trust in the risk management and assessment system (*see* Löfstedt and Bouder, 2017 for a discussion; Johnson and Slovic, 1998; Beck *et al*. 2016; National Academy of Science, 2016).

Going further, a closely connected strand of the literature has examined important issues with public participation and deliberation that process transparency by itself would be unlikely to resolve (Löfstedt, 2004). Four main issues are highlighted here. First, there are important time and resource limitations. Public participation can be costly and decision-makers cannot feasibly discuss all aspects of the risk assessment and management process for every risk issue (Rowe and Frewer, 2000; Abelson and Gauvin, 2006). For example, one national debate on genetic modification held by GM Nation in 2003 was initially estimated to cost around £250,000 but quickly escalated to over £600,000, which excluded hidden financial costs as well as additional time burdens on central government (Momenta, 2003). Second, there are clear difficulties with recruiting participants (Löfstedt, 2004). Combined with low participant response rates that can drop below 1% (Löfstedt, 1999; Renn, 2008), issues of self-selection bias (and unrepresentative samples) can create biases towards particular groups and agendas (Löfstedt, 2004; Pidgeon *et al*. 2005). Third, participants can have fundamentally contradictory principles, beliefs and ideals resulting in few ways of reconciling risk controversies and little hope of coming to mutual agreements (Pellizzoni, 2001). Fourth, often debates and discussions favour what should be done over what can be done without fully recognising practical limitations (Rozzi, 1997; Coglianese, 2007).

Due to these issues and more several scholars have demonstrated that there are many barriers, obstacles and limitations to implementing effective process transparency (and participation in general) (Petts and Brooks 2006; Wesselink *et al*. 2011). There have also been many different ways that organisations have adapted to process transparency requirements and subsequently changed their practices. For example, Rothstein (2013) argues that the UK Food Standards Agency has often coped and adapted to public participation pressures rather than truly foster public engagement and participation in decision-making despite receiving good reviews from consumer groups (e.g. the Consumers Association's '*Which?'* magazine). For Pidgeon and Rogers-Hayden (2007), attempts to engage the public upstream and in the risk characterisation and assessment process has also been problematic (also *see* National Research Council, 1996). Ultimately, integrating public participation into risk-decision-making has largely failed to live up to expectations (Rossi, 1997; Flyvberg and Richardson, 2002; Löfstedt, 2004; Petts and Brooks, 2006; Coglianese, 2007) and process transparency is not problem free (Bijker *et al*. 2009; Vos, 2009).

(3.1.3) Input mechanisms

Over the past 10 years, many new input transparency policies have been introduced by regulatory agencies (*see* Way and Löfstedt, 2016; also *see* Fung *et al*. 2007: 12-13). Environmental regulatory domain policies have received some of the most attention and include the US Toxics Release Inventory (TRI) (Stephan, 2002; Kraft *et al*. 2011), the Global Reporting Initiative (GRI) (Dingwerth and Eichinger, 2011) and amendments to the US Safe Drinking Water Act (Environmental Protection Agency, 1996). Policies from outside the environmental realm include EMA's clinical study reports transparency policy (Chapter VI) (EMA, 2014b), the FDA's adverse drug reaction reports policy (Chakraborty and Löfstedt, 2012), EFSA's Data Warehouse Project (Url, 2013; Way and Löfstedt, forthcoming), the US Food Safety and Inspection Service's (FSIS) data release project (FSIS, 2016), and many others.

For all of these policies, the main mechanism for enhancing input transparency has centred on publishing the data and information that underpins risk regulation online (Way and Löfstedt, forthcoming). This includes a collective wealth of information relating to, for example, clinical trials and side effects (e.g. in pharmaceutical regulation), genetically modified organism risk assessments (e.g. in food safety regulation), hospital mortality rates (e.g. in health and social care regulation), industrial emissions data (e.g. in environmental regulation), crime statistics (e.g. in policing), road safety accidents data (e.g. in transport regulation), and so on. Yet, despite the wave of new input policies introduced in recent years, they have received surprisingly little attention in the academic literature (*see* Cucciniello *et al*. 2017), especially when compared with output and process policies. The following section provides a more comprehensive review of input transparency policies as they will become the central focus of the empirical chapters of this thesis.

(3.2) Focusing on input transparency

At least three main perspectives on input transparency policies have taken prominence in the fragmented literature: soft risk regulation (2.3.1); scrutinising regulatory data (2.3.2); and data quantity and quality (2.3.3).

(3.2.1) Soft risk regulation

One perspective in the literature centres on the idea that uploading informational inputs online can act as a form of 'soft' risk regulation (Fung *et al*. 2007; Mitchell, 2011; Kraft *et al*. 2011; Gupta and Mason, 2014). This is labelled hereafter as 'regulation by disclosure' but has also been referred to as 'governance by disclosure', 'regulation by revelation', 'targeted transparency', 'information governance', 'information as regulation' and others (Stephan, 2002; Fung *et al*. 2007; Gupta. 2008; Mitchell, 2011; Gupta and Mason, 2014). In this literature, transparency is understood as a "light handed" and innovative regulatory tool that can be used to overcome the shortcomings of traditional command and control approaches (Kleindorfer and Orts, 1998; Kraft *et al*. 2011). Notably, the latter is often criticised for being too constraining, costly and unreasonable (Bardach and Kagan, 1982) or as Coglianese (2016) clarifies:

> *"Such objections [to command and control regulation] are loudest when rules inflexibility require every regulated entity to take the same actions – or adopt the same technology fixes – even if under some circumstances, or for some entities, the required action or technology might be expensive, ineffectual, or even counterproductive".*

Many transparency by disclosure policies work by requiring targeted actors – such as producers of goods and services – to "disclose information about their activities that they would prefer not to disclose" (Mitchell, 2011: 1885). However, other policies – and the focus of this section – require the same actors to accept disclosure of such information by others (e.g. the regulators) (Mitchell, 2011). For example, the US Environmental Protection Agency's Toxics Release Inventory requires industrial emissions polluters to publish pollution data online (Kraft *et al*. 2011). In contrast, the regulators could publish this information themselves (e.g. by uploading pollution permits and other regulatory data online). Although there are important differences between who discloses the information, the central argument for all regulation by disclosure policies is broadly the same (Fung *et al*. 2007). Disclosing informational inputs relating to products and services – such as data on pollution, food safety, medicines, hospital mortality rates, police crime statistics etc. – is expected to induce targeted actors (e.g. producers of goods and services) to change their behaviour and reduce specific risks to the public (Stephan, 2002; Dingwerth and Eichinger, 2010; Mol, 2010; Mitchell, 2011; Gupta and Mason, 2014).

This is expected to work in two stages. In the first stage, disclosing informational inputs is expected to empower the public to reduce risks to their health and/or the environment by enabling them to choose safer and better products and services (Fung *et al*. 2011). In other words, information is disclosed via a publicly accessible web-portal and is subsequently perceived by the public – such as by individuals reading data online (directly) or via intermediaries such as the media or NGOs (indirectly) (Mitchell, 2011) – thus resulting in a better informed public. This is premised on the understanding that consumers have imperfect information about (powerful) actors in society (e.g. industry and government) (Stiglitz, 1999), which creates disparities in information about risk (*see* Fung *et al*. 2007: 31-33 for a discussion). Reducing these information asymmetries is therefore expected to empower consumers to make more informed decisions (Stiglitz, 1999; Michener and Bersch, 2016).

Depending on the regulatory context (and the data released) the public can make many safer and better decisions. Employees can choose safer working environments (e.g. with workplace hazards data), patients can choose better performing hospitals (e.g. with hospital performance data), environmentalists can boycott products made in high polluting industrial facilities (e.g. with industrial pollution data), parents can choose safer neighbourhoods (e.g. with crime data), drivers can choose safer cars (e.g. with accident data) and so on (Fung *et al*. 2007: 12-13). For example, a key recommendation in the Francis Review[13], a UK public inquiry into serious failings at the Mid-Staffordshire National Health Service (NHS) Foundation Trust, was that the hospital and its staff should allow "true information about performance and outcomes to be shared with staff, patients and the public" (Francis, 2013: 75). One reason for providing such information – that is also received by the healthcare regulator or commissioner – is to enable the public "to compare relative performance" between hospitals and thus reduce information asymmetries (ibid, 2013). Therefore regulation by disclosure transparency policies can be classified as capacity building tools, defined as "policies or programs that increase the ability of people to act on their concerns" (Stephan, 2002: 191).

In the second stage, the actions of consumers – or at least the expected actions of consumers – are hoped to prompt targeted actors to adopt less risky behaviour. Employers might create safer working environments, hospital managers might improve patient safety, industrial facilities might reduce pollution levels, manufacturers might develop safer cars, and so on. For example,

[13] The full title of the report is '*The Mid-Staffordshire NHS Foundation Trust Public Inquiry*'.

in the environmental context, the 1998 Aarhus convention seeks to "reduce the incidence of environmental externalities by rectifying information deficits and asymmetries" (Mason, 2014a: 87). Then consumers can choose between better and less risky products and services. Mitchell (2011) explains several reasons why targeted actors might change their behaviour. This includes organisations (*see* Mitchell, 2011: 1886):

1. becoming aware of their own (poor) behaviours (e.g. in preparation for public disclosure);
2. becoming aware that their behaviours may not be appropriate (e.g. the fact that the regulators feel disclosure is necessary);
3. having to explain or attend to behaviours that they otherwise might ignore and/or;
4. revealing information to other producers (e.g. concerns that they are underperforming compared to competitors).

However, the most widely discussed mechanism is that disclosure is expected to shock the public and shame producers of goods and services into changing their activities (Stephan, 2002; Fung *et al*. 2007; Mitchell, 2011; Weil *et al*. 2013). As Roberts (2012) puts it: "leak, publish and wait for the inevitable outrage". Assuming the information made publicly available conflicts with the public's prior expectations (Mitchell, 2011), it has the potential to shock them and raise their perceptions of risk (Stephan, 2002). In turn, producers can be shamed into changing their activities and reduce risks from their products and/or services. For example, producers could lose, or at least expect to lose, custom or suffer reputational damage. Several authors have also emphasised that the shock and shame mechanism is more likely to work through intermediaries rather than consumers themselves (Kraft *et al*. 2011; Gupta and Mason 2014: 16-17). For example, intermediaries could interpret the disclosed information, communicate it to the public and gain support for shaming producers (Kraft *et al*. 2011). Taken together, by disclosing information, the public are expected to be "empowered to take decisions, without [the regulators] specifying what these decisions should be, and that the aggregate effect of those decisions will lead producers to adopt (or maintain) [less risky behaviour]" (Mitchell, 2011).

(3.2.2) Scrutinising regulatory data

A second perspective on input transparency centres on the re-use and re-analysis of regulatory data. This literature can be strongly connected to the two concepts of accountability (Bovens, 2008; Hood, 2010) and legitimacy (De Fine Licht *et al*. 2014), as well as long term declining levels of public trust in risk regulation (Löfstedt and Bouder, 2014; Tuler and Kasperson, 2014). The central argument is that publishing the evidence that underpins decision-making online is essential for facilitating external scrutiny (e.g. by external experts and the public). Outsiders can "see" the data for themselves without anyone else interpreting what that evidence means (Way *et al*. 2016).

Central to this fragmented literature is the understanding that a substantial amount of input information is not currently available beyond the regulators and industry (Löfstedt *et al*. 2011). This is especially true for privately-funded, rather than publicly-funded, research such as data collected in support of licensing applications, pollution permits or other regulatory activities (McGarity and Wagner, 2008; Michaels, 2008; Goldacre, 2008; Shrader-Frechetter and Oreskes, 2011). For example, many privately-funded studies are not reported in peer review journals (Song *et al*. 2010; Goldacre, 2012; Dwan *et al*. 2013), yet are used as key evidence in support of regulatory decision-making. Although there are many reasons for this, a main one centres on traditions of confidentiality and privacy (*see* Section 2.3.3), which some critics have argued favour industry too strongly (Roberts, 2006).

Advocates of full input transparency have provided many reasons why all data and information used in risk regulation should be make publicly available online. One argument is that outsiders need input data in order to judge whether the regulatory evidence base is robust and unbiased (e.g. risk assessment data). In particular, outsiders – and especially the scientific community – need to be able to see the actual risk assessments and judge whether privately-funded evidence is credible (also *see* Silbergeld, 1993; Montague, 2004; Forbes *et al.* 2016: 1069). Although it may indeed be of high quality, critics argue that outsiders cannot judge this for themselves (Shrader-Frechette and Oreskes, 2011). In turn, high quality expert scrutiny is expected to provide the regulators with a more robust evidence base for decision-making and added capacity for evaluating the quality of the evidence.

In arguing for input transparency, many advocates have criticised privately-funded research and data (Abraham and Lewis 1999; Michaels, 2008; Song *et al*. 2010; Corporate European Observatory, 2015; Forbes *et al*. 2016). In the pharmaceutical domain, critics have argued that studies funded by industry are more likely to produce positive than negative results (Angell, 2004; Song *et al*. 2010; Goldacre, 2012; Dwan *et al*. 2013). In risk assessment more generally, Michaels (2008) argues that private risk assessment companies (e.g. Exponent or ChemRisk) produce biased results that have, for example, denied the risks of hazardous pollutants, endocrine disrupters, harm from cigarettes, asbestos, and many others. These arguments are also accompanied by trust-eroding news stories and events where industry has undertaken overtly fraudulent activities that seriously damage credibility. This includes the 2016 Volkswagen clean diesel engines fraud (Crete, 2016) and companies being fined huge sums for creating inaccurate findings (e.g. industry hiding results) (*see* e.g. Jack, 2014).

A second closely connected argument has been that regulatory data needs to be scrutinised whether it has been funded by industry *or not* (Forbes *et al*. 2016). In particular, some advocates have pointed to issues with the scientists themselves. This includes pressures on scientists to publish favourable results such as for recognition, career development or funding requirements (Forbes *et al*. 2016). Others point to scientists acting inappropriately, fraudulently or with highly questionable conflicts of interest (Fang and Casadevall 2011; Ebrahim *et al*. 2014). For example, critics have pointed to 'Climategate', that is, the University of East Anglia climate change unit email controversy, and the retraction of Andrew Wakefield's article fraudulently linking the Mumps Measles and Rubella vaccine to autism (Boyce, 2007). Retraction watch, for example, is a blog that reports on the retraction of scientific papers and whose website provides on-going examples of incidents of poor researcher conduct (*see* www.retractionwatch.com).

In support of these arguments, some researchers have pointed out that much scientific research is not replicable (*see* Buthe *et al*. 2015 for a discussion; Bohannon, 2012). This is closely linked to an additional strand of the literature that focuses on open data and innovation whereby open science is expected to enable attempts to replicate study findings (McKinsey and Company, 2013; Madelin and Ringrose, 2016). Therefore one main argument is that enabling external scrutiny is needed in order to allow outsiders to try and replicate studies themselves (Bohannon, 2015). For example, Martin Pidgeon of the Corporate European Observatory (CEO), a

European research and campaign group, criticised EFSA for being irresponsible with regard to transparency and information disclosure:

> *"Transparency isn't only needed to improve public confidence in EFSA's work but also in order to ensure EFSA's assessments are based on sound science. A fundamental principle of science is replicability: the methodology and results of the industry tests need to be made public so that other scientists can replicate the test and see if they get the same result."* (CEO, 2013).

There are therefore many arguments for publishing informational inputs that centre on criticisms of industry data and the science and scientists that underpin decision-making.

A third argument is that publishing informational inputs online can enable outsiders to scrutinise not just the evidence itself but the regulators' *interpretation* of that evidence (Dudley and Weigrich, 2015: 3). The central idea is that transparency can "empower the public to observe the actions of the regulators to whom they have delegated power or of other powerful actors in society" (Mitchell, 2011: 1885). For example, uploading informational inputs can enable those outside the regulatory process to scrutinise the regulators' choice of evidence, interpretation of that evidence and whether there were any conflicts of interest. As Baxter (2012: 147) puts it: "greater disclosure all round would at least enable other stakeholders and the media to focus a spotlight on improper collusion". Input transparency is expected to enable outsiders to identify whether the regulators succumbed to "selective or biased attention" (Lodge, 2004: 126) and/or self-interested action (Baxter, 2012). Some scholars have gone further by arguing that the regulators will also "behave better" if they know they are being "watched" (Meijer *et al*. 2015). As Dudley and Weigrich (2015: 3) put it:

> *"…when methods of regulatory analysis are prescribed and regulators have to publicly report the data, models, assumptions, and technical rules on which regulatory proposals are based, public scrutiny can motivate them to be prudent about using the evidence in general and conducting cost-benefit analysis in particular".*

Similar to criticisms of privately-funded research, input transparency advocates often support their arguments by citing various high-profile scandals and criticisms that have been linked to risk regulators. This includes accusations of revolving door policies and regulatory capture by industry, which occurs when "agencies tasked with protecting the public come to identify with the regulated industry and protect its interests against those of the public" (Carpenter and Moss,

2013). Examples of these scandals and criticisms are numerous. Ex-EU commissioner for Health and Consumer Policy, John Dalli, was linked to a tobacco lobbyist while responsible for introducing tougher anti-smoking legislation (Gotev, 2016). A senior ex-EMA pharmacovigilance risk assessment committee (PRAC) member, Silvio Garattini, criticised the agency for being too cosy with industry (Chapter V) (Garatini, 2007). Volkswagen appointed ex-EU climate commissioner Connie Hedegaard only a few months after the 2016 emissions scandal (Eriksson, 2016). Jose Manuel Barosso, joined Goldman Sachs shortly after stepping down as EU Commission president (Macdonald and Baczynska, 2016). Thomas Lönngren joined a consultancy firm called NDA shortly after stepping down as EMA Executive Director (Chapter V) (Makhasvilli and Stephenson, 2013). At EFSA, conflicts of interest policies were heavily criticised in 2010 after one of its committee chairs, Diana Banati, was linked to an industry lobby group, the International Life Sciences Institute (Boseley, 2014a). After resigning from the institute and maintaining her position at EFSA, she went on to resign as chair at EFSA and become head of European policy at the lobby group (Boseley, 2014a).

(3.2.3) Data quantity and quality issues

A third perspective on input transparency relates to the quantity and quality of data and information published online. One important question centres on the desirability and feasibility of uploading *all* input information (Gupta and Mason, 2014). This is hereafter referred to as 'full input disclosure'. On the one hand, there are many aforementioned reasons why full input disclosure might be beneficial (e.g. relating to regulation by disclosure or scrutinising regulatory evidence). The public have a right to information and access to documents, which is enshrined into law (e.g. Regulation (EC) No 45/2001 of the European Parliament and Council) (Birkinshaw, 2006; Zarsky, 2014: 123). Advocates of open government, open data, information innovation, and the so-called "big data" movement also often stress that full disclosure is necessary (although *see* Zarsky, 2014) (Mayer-Schönberger and Cukier, 2013). Many have argued, for example, that limiting what information can be made available would limit the promises of open data (Bertot *et al*. 2014).

On the other hand, there are valid reasons why full input disclosure may not be desirable or feasible (Lord, 2006; Birchall, 2011; Gupta and Mason, 2014). One argument is that there are important trade-offs between the overall costs of releasing vast quantities of regulatory

information and burdens on regulatory authorities and their resources (Grimmelikhuijsen, 2012; Meijer *et al*. 2015). For example, the UK FOI Act (2000) has been criticised for imposing unnecessary and excessive burdens on public authorities (*see* UK Ministry of Justice, 2012). One issue is that excessive resource consumption can result in the regulators being unable to commit resources to other, perhaps more effective or useful, public policy interventions (Etzioni, 2010). As Meijer *et al*. (2015) put it:

> *"…the benefits may merit substantial investments in transparency, but there are also opportunity costs. Money spent on transparency cannot be used to strengthen other citizen participation, checks and balances or learning mechanisms in different—and possibly more effective—ways".*

Therefore transparency is not cost-free and opportunity costs need to be taken into consideration when advocating full input disclosure (Etzioni, 2010).

A second and much more widely discussed argument is that full input disclosure is unattainable and undesirable due to the merits of confidentiality, privacy and anonymity[14] (O'Neill, 2006; Lord, 2006; Birchall, 2011; Gupta and Mason, 2014: 15 Heald, 2006: 64; Zarsky, 2003; 2014). Full input transparency is limited by legal obligations. For example, EFSA's '*Transformation to an Open EFSA'* discussion paper makes clear that the agency is obliged and committed to protect privacy and commercially sensitive information in order to remain compliant with EU laws set out in its founding regulation (*see* article 38 and 39 of Regulation (EC) No 178/2002). Similarly, the UK FOI Act (2000) includes the requirement that "when a request is made about a private citizen, nondisclosure is mandated if the invasion would be clearly unwarranted" (Zarsky, 2003: 997). Rather than reviewing the now extensive literature on confidentiality, privacy and anonymity, the importance of these three distinct but related objects is briefly exemplified.

Confidentiality refers to the limits that are placed on who is authorised to use input data and information. Although there are many reasons for confidentiality (e.g. relating to national defence and security) (Halstuk et al. 2006), one main argument is that confidentiality can protect the market and economy (Zarsky, 2014). This often centres on commercial confidentiality and the understanding that "businesses require a minimal level of privacy to

[14] To be clear, these three objects are related but distinct (Heald, 2006b).

allow them to refrain from revealing their business practices, thus facilitating an innovative and competitive market" (Zarsky, 2003: 1002). For example, much input information contains data collected by a company that would be valuable to its competitors. This has led some commentators and industry groups to argue that if commercial confidentiality is not maintained then this could result in "free riding" (Eichler *et al*. 2013)

Privacy refers to the affairs of the individual and the state of being free from public attention (Heald, 2006: 65; Birkinshaw, 2006). Input documents can contain a broad range of personal information "that is identifiable to that individual" including, but not limited to, an individual's health, genetic code, family, sexual preferences, credit history, eye colour, income, and so on. If this information is not protected, then its publication may lead to important issues. According to Zarsky (2003, 2014), this includes:

1. criminal misuse or abuse of personal data (e.g. blackmail or exposing vulnerable individuals);
2. problems arising from errors in databases (e.g. unfair treatment of specific individuals);
3. the use of personal data to discriminate between users (e.g. aggressive price discrimination) and;
4. the use of such data by content providers and advertisers to manipulate and impinge on personal autonomy (e.g. unfairly persuading or manipulating individuals).

For example, one of the UK's largest NHS-approved online pharmacies, Pharmacy2U, received a £130,000 fine for breaching the UK Data Protection Act by selling personal data from 21,000 NHS patients and online customers (Green, 2015). Highlighting the potential for misuse, the information was, in turn, bought by (1) an Australian lottery company that is subject to an investigation about trading standards and (2) a UK charity that used the details to ask for donations from people with learning difficulties (*see* Green, 2015).

Anonymity refers to the state of being unidentifiable as an individual and, as Zarsky (2003: 1024) puts it, involves "disconnecting the information collected from the individuals to whom it pertains". Anonymising input documents has been viewed as a way of overcoming confidentiality and privacy issues by removing identifiable information such as through redacting information with black boxes (e.g. EMA, 2016b). This might include redacting

names, addresses, and other personal information. However, even the most sophisticated anonymisation techniques are imperfect due, in particular, to resource burdens from anonymising data (e.g. on those redacting information) and arguments that anonymisation is not actually possible (Abbasi and Chen, 2008). For example, Narayanan *et al*. (2012) discuss several ways of identifying individuals in documents that have redacted information such as through automated linguistic stylometry, which can be used to compare writing styles in a document (e.g. writing patterns) against texts that haven't been anonymised (e.g. published articles, blogs etc.)

These arguments and others have led many commentators to state that that the full disclosure of information is unattainable and/or undesirable (Gupta and Mason, 2014: 15). For every doctrine there is almost always a counter-doctrine (Hood, 2006b) or as O'Neill (2002: 18) puts it:

> *"We fantasise irresponsibility that we can promulgate rights without thinking carefully about the counterpart obligations, and without checking whether the rights we favour are consistent".*

Therefore many therefore view 'full' or 'maximum' input transparency as "naive" (e.g. de Fine Lincht *et al*. 2013) and, in many cases, would rather identify an optimal 'level' (Hillebrandt *et al.* 2014) such as through partial disclosure (Gupta and Mason, 2014). Furthermore, although some authors have contextualised these counter-arguments as responses to transparency pressures and organisational defence strategies (Hood et al. 2001; Roberts, 2006; Hood, 2007; Pollitt and Bouckaert, 2011), others have strongly argued that the full disclosure of informational inputs can damage privacy and confidentiality (Zarsky, 2003, 2014; O'Neill, 2006). Ultimately there are important limits and policy considerations directly relating to the quantity of input information that the regulators can legally or feasibly release.

Along with quantity, a large scholarship has also debated input data quality issues. This literature has centred on the desired attributes of disclosed input information, which include, but are not limited to, whether it is accessible, comprehensible, comparable, accurate, actionable or relevant (Gupta and Mason, 2014). As discussed in the introductory chapter (section 1.2), "For transparency to be effective, there must be receptors capable of processing,

digesting, and using the information" (Heald, 2006: 35). There are, however, many issues relating to the quality of data, which mean that these criteria may not be met.

Three main examples can exemplify the importance of data quality (Roberts, 2006). First, input information may be incomplete or unreliable due to, for example, poor record keeping or data manipulation (Roberts, 2006). One well-known practice in accounting and finance is window dressing where, for instance, bank managers "manipulate accounting values around quarter-end reporting dates to make accounts appear more favourable" (e.g. by making short-term financial transactions) (Allen and Saunders, 1991: 386). Second, input information may be too complicated for recipients to process or digest. In other words, outsiders may lack the capacity to interpret or use the disclosed data. The implicit rationale behind input transparency is: "Information is received; it is posted online; and it readily finds an audience, which in turn makes sense of it" (Roberts, 2006). This logic assumes that information recipients can understand the information and have incentives, capacities and alternatives that can foster changes in their behaviour (Mitchell, 2011). Recipients must also be interested in the information in order to achieve the regulators' goals. As Mitchell (2011) explains:

> *"…the causal chain linking increased transparency to behavioural change by targeted actors often is broken by information recipients who lack any interest in, or have interests that run counter to, accessing or responding to the new information being generated".*

Third, input information may not be actionable. Providing too much information can drown recipients in disclosure (Gupta, 2008). 'Snowing' is a term used for when organizations, intentionally or otherwise, disclose vast amounts of information with little quality control thus reducing the effectiveness or usability of transparent information (Hood, 2007). For example, Etzioni (2010: 5) comments:

> *"...a 47-page mortgage can lull people into a false sense of security, as they mistakenly believe that more details means more honesty. […]. If the industry were required to offer a standard mortgage with easy-to-understand terms, consumers might receive less direct information but would gain information they would be able to digest and use".*

Moreover, these data quality arguments are also relevant to input transparency *intermediaries* who interpret such information "thus acting as receptors" (Heald, 2006: 35; Etzioni, 2010: 12-14; Mitchell, 2011; Gupta and Mason, 2014: 16-17). In the risk communication literature these

intermediaries might be categorised as 'information channels', defined as "a conveyance device that collects information from a source or sources, repackages it and then disseminates it" (Dunwoody and Griffin, 2014: 222). One issue is that in order for transparency to be effective "complex infrastructures of monitoring and verification are needed to render disclosed information usable" (Mitchell, 2011). This is important as intermediaries are more likely to have the required time, expertise and resources to understand the information and convey it to ill-equipped outsiders (e.g. those who lack the expertise or time).

A second issue is that, in order to fulfil their role, intermediaries will inevitably have to first repackage and then convey the input information (Etzioni, 2010). As Dunwoody and Griffin (2014: 222) explain:

> *"[The] primary goals of mediated channels are to be highly selective in choosing information, and then to embed the selected information in narratives that seek to summarise, analyse or be persuasive about the events or processes of interest".*

This role of intermediaries for enhancing transparency has led many scholars to argue that risk information can easily be misinterpreted or repackaged in a way that suits the intermediaries that may go against the regulators' advice or expectations (O'Neill, 2006; Manson and O'Neill, 2008; Etzioni, 2010; Way *et al*. 2016). Some scholars have argued that the public, who are often ill-equipped to make first order analyses of data made available through transparency requirements, will receive one-sided arguments from experts and critics of regulators such as from the media or campaigning organisations (O'Neill, 2006; Mason and O'Neill, 2008; Etzioni, 2010).

These two issues can be exemplified with an illuminating example (*see* Löfstedt and Way, 2016a; also *see* Etzioni, 2010: 12-14 for further examples)[15]. Over 20 years after the Toxics Release Inventory was first established, the US's largest disclosure programme that releases pollution data on thousands of facilities across America annually, *USA Today* (2008) released an article documenting widespread pollution levels surrounding just under 128,000 American schools (Kraft *et al*. 2011). The reporters concluded that "the potential problems [of chemical risks] that emerged were widespread, insidious, and largely unaddressed" (Gilbert 2008 In: Kraft *et al*. 2011: 187). However, after "considerable review", the Department of Natural

[15] Note: this example was first reported by the author in Löfstedt and Way (2016).

Resources found that the reporters had misinterpreted and poorly analysed the data from the publicly available Toxics Release Inventory database (Kraft, *et al* 2011: 216). Yet, the report still caused widespread concern from parents across America, which was not easily relieved by refuting the news agency's findings (Kraft *et al*. 2011).

(3.3) Building public trust

Beyond the many arguments specific to different transparency mechanisms, there are also several main goals of transparency that are relevant to all objects and mechanisms (Section 2.1.3). This includes the goals of promoting meaningful public participation, enhancing legitimacy and enabling the re-use of data for experts outside the regulatory process (section 2.1). For example, when re-analysing input data (e.g. for external scrutiny) a data analyst will need to know what decisions the regulators made in order to judge whether they came to accurate conclusions. Although there are indeed many goals, for many regulatory authorities, the overriding goal of enhancing transparency is to build public trust in risk regulation. For example, after announcing a new input transparency, the EMA made clear:

> *"[The Agency] has committed to continuously extending its approach to transparency. […]. The Agency has embarked on this process because it believes that the release of data, making it accessible to all who wish to see it, is about establishing trust and confidence in the system"* (EMA, 2015a: 1).

Indeed, building public trust through transparency is viewed as the ultimate goal for many organisations outside of risk regulation (Grimmelikhuijsen, 2010). Many of the arguments relating to trust are implicit in the previous sections. Therefore the purpose of this section is to make the main arguments for and against the effects of transparency on trust explicit.

Several authors have distinguished between transparency optimists and pessimists, primarily because their arguments are often based on anecdotal rather than empirical evidence (Hood, 2006b; Grimmelikhuijsen and Meijer, 2012). Both optimists and pessimists recognise the importance that information plays. Specifically, providing more information on regulatory decision-making (e.g. posting safety-related documents online) is understood to have either a positive trust building effect (transparency optimists) or a negative, trust eroding effect (transparency pessimists).

One main optimist argument can be categorised as the 'extended citizen-knowledge effect' (MacDonald, 2006). When transparency is lacking, outsiders (e.g. the public) are understood to be ill-informed about regulatory decision-making (e.g. the rationale for why a course of action was taken) (O'Neill, 2006). They are thus poorly placed to judge the trustworthiness of the regulators and their decisions and whether the regulators are deserving of their trust (O'Neill, 2006). For instance, Kasperson (2014: 4) highlights that low trust levels can be particularly challenging when "the risk communicator is not well known or [is at least perceived to be] closely linked to the risk bearer". In contrast, when transparency and openness are present, outsiders are expected to be in a fully informed position to judge effectively the trustworthiness of the regulators (Etzioni, 2010), or as O'Neill (2006) puts it: outsiders will be able to "secure a basis for more trustworthy performance". They will be able to observe the regulators' actions and whether they agree with, for instance, their decision-making rationale. 'Outsiders' will also better understand the workings of regulatory agencies including the limits of regulatory activity, how responsibilities are divided amongst different groups (e.g. industry and regulators) and that many risk issues are highly complicated and require difficult regulatory decisions to be made (section 2.2.2) (Grimmelikhuijsen, 2010: 177). "Better informed citizens are [therefore] expected to have more trust" (Hood, 2006b) as they will be viewed positively (e.g. open, honest, competent) in an "extended citizen knowledge effect" (MacDonald, 2006).

A closely connected 'optimist' argument is that transparency will create cultures of openness, which will be perceived as trustworthy by outsiders (Roberts, 2006; EFSA, 2014). When transparency is lacking the regulators are expected to act poorly (e.g. corruption, mismanagement etc.) as they will know they are not being 'watched' by those outside the regulatory process (Brandeis, 1913; Prat, 2006; Bauhr and Grimes, 2014). For instance, Transparency International often argues that a lack of transparency can result in corruption, mismanagement and poor performance (Transparency International, 2016). Therefore a lack of transparency is understood to contribute to a culture of secrecy, which Roberts (2006) notes was judged to be a central cause of many major regulatory failures such as the BSE crisis. However, when transparency is present the regulators will know they are being observed or watched and are expected to behave better, or as the 18th Century Philosopher, Jeremy Bentham, stated in his famous dictum: "the more strictly we are watched, the better we behave [and this is] an indisputable truth…that is one of the corner stones of political science" (Bentham, 2001: 277 In: Hood, 2007). The central understanding is that 'sunlight' and public

'surveillance' will not allow regulators to conceal or 'hide' information leading, in turn, to better regulatory behaviour and management. Transparency as sunlight is therefore expected to create a 'culture of openness' (Hood, 2006b), which can combat cultures of secrecy that are defined by concealment, corruption and poor regulatory performance (Birkinshaw, 2006). In turn, the regulators are expected to be perceived positively and will be deserving of public trust.

Taken together, the extended knowledge effect and cultures of openness arguments are understood to work in synergy. Transparency throughout the regulatory process is expected to allow the public to observe, watch and judge the trustworthiness of regulators (i.e. extended citizen-knowledge effect), while the regulators themselves are expected to behave better and therefore provide more reason for 'outsiders' to place trust in them (i.e. culture of openness argument) (O'Neill, 2006; Etzioni, 2010). In turn, the regulators are expected to be perceived positively and as trustworthy because outsiders will recognize that they are competent, honest, and open public agents that are deserving of their trust. As Hood (2006b) explains: regulatory agencies "adopt a culture of openness, citizens end up knowing more, and trust in democratic government goes up".

However, although there are many optimistic transparency arguments, there are also many 'pessimistic' ones (O'Neill, 2006; Etzioni, 2010; Hood and Heald, 2006). So-called transparency 'pessimists' have put forward many arguments focusing on potential counterintuitive and unintended effects of transparency on trust. One central expectation is that transparency will lead to scandals of misinformation and public confusion of regulatory decision-making, which will, in turn, lead to negative trust eroding effects. Onora O'Neill, in particular, has argued that transparency requirements primarily benefit 'outside' groups and external critics – who do not have the same requirements imposed on them – who may misuse or 'spin' the information made available:

> *Transparency requirements can benefits expert 'outsiders' by enabling them to access information about the performance of intuitions and their officeholders. This is particularly helpful to expert critics of government, business and professional performance. Expert critics often have the time and ability to grasp and use the information in ways that the wider public does not. Transparency is therefore particularly useful to the media and to campaigning organisations, who can discover information that bears on others' performance (while they themselves are generally exempt from like transparency requirements)."* (O'Neill, 2006: 88).

A key understanding with this argument is that the public are "ill-placed" to make direct judgements of regulatory decision-making data (e.g. lack of time and expertise) and will therefore have to rely on second-order judgements made by those that are likely to want to criticise regulators in the first place (e.g. critics or campaigning organisations) (*see* section 2.3.3). This may include spinning, misinterpreting or 'poorly' analysing information about events and/or processes made publicly available. Other scholars have gone further by arguing that the regulators could, in turn, be justly and unjustly continually blamed for poor management issues and nit-picking of policies leading to an erosion of public trust (Worthy, 2010; Bovens, 2003).

A second argument is that 'outsiders' may become disenchanted with the reality of regulatory decision-making. For example, backstage discussions made public by 'fishbowl' style policies, where all activities and conversations of decision-makers are monitored, might result in public disenchantment of decision-making as regulators may be seen as bickering and muddling through the decision-making process rather than coming to clear and certain decisions (section 2.2.2). In turn, the regulators may be seen to be less competent, which will result in declining public trust. Therefore some have argued that some degree of 'backstage' activity has to take place in order for decision-makers to maintain and strengthen public trust (Bijker *et al*. 2009). In other words, without the ability to conduct these affairs freely, the regulators may look weak or incompetent, which in turn, is expected to erode trust.

A third main 'pessimist' argument is that transparency will result in behaviour changes that will directly affect the usability and usefulness of information resulting in confusion and an erosion of public trust (Hood, 2007). For Hood (2006b, 2007), this represents a futility and jeopardy argument that is pessimistic in expecting limited and negative effects of transparency on trust. For example, when a banker opts to make a phone call or meet a colleague in private rather than send an e-mail (e.g. to avoid FOI disclosure requirements) then less information is created that can be made transparent. This would mean that the really important information would not be observable to the public and the organization would avoid blame. Other more perverse behavioural changes might include organizations intentionally keeping poor records or flooding recipients with too much information (e.g. snowing or window dressing) (see Section 2.3.3 for a discussion). For Tsoukas (1997) one of the key issues with transparency is that more information will *de-facto* result in less understanding, confusion and, in turn, erode

public trust. Therefore there are many theoretical arguments for and against the ultimate goal of building public trust in risk regulation.

(3.4) Concluding remarks

This chapter reviewed the fragmented literature on transparency in risk regulation. After first offering an organising typology, a wide range of policy mechanisms that are designed to make different regulatory objects more transparent were identified and debated. These were sub-divided into three categories: output mechanisms, process mechanisms and input mechanisms. First, the multiplicity of output transparency mechanisms introduced by risk regulators was first directly linked to the sub-field of risk communication. These range from written information (e.g. press statements, information leaflets and committee reports) (Morgan *et al*. 2002; Fleishman-Mayer and Bruine de Bruine, 2014; Way *et al*. 2017) to infographics (Spigelhalter *et al*. 2011), visual and audio tools (Downs, 2014) and social media more generally (Moorhead *et al*. 2013; Brossard, 2013; Neeley, 2014). Although these output mechanisms – or risk communication 'tools' – were not reviewed individually, it was made clear that the extensive risk communication literature has provided many arguments for and against introducing different mechanisms for enhancing output transparency and in different regulatory contexts.

Second, the literature on procedural process transparency mechanisms – that has primarily centred on publishing procedural documents online such as conflict of interest statements or scientific guidance documents – was reviewed. Despite many regulatory bodies introducing such policies, only a handful of studies have examined the advantages (e.g. Piotrowski and Borry, 2010) and disadvantages (e.g. Lowenstein *et al*. 2014) of doing so. In contrast, operational process mechanisms have received the lion's share of academic attention with most articles debating the publication of meeting minutes online or the more radical mechanism of web-streaming meetings live. While some scholars have strongly advocated these mechanisms (e.g. to increase the public's willingness to accept regulatory decision-making) (De Fine Licht *et al*. 2014), others have demonstrated that there are important issues, challenges and limitations with full operational process transparency and opening up decision-making to all outsiders (e.g. paralysing the regulatory process) (Bijker *et al*. 2009; Vos, 2012).

Third, the main mechanism introduced by risk regulators for enhancing input transparency has been to publish the data and information that underpins decision-making online. Notably, these policies have become increasingly popular over the past 10 years with risk regulators introducing a collective *tsunami* of new policies. Two main arguments for introducing such policies are that input transparency can act as a form of soft risk regulation (i.e. regulation by disclosure) and can enable outsiders to scrutinise the data and information that underpins decision-making including the regulators' interpretation of the evidence. On the other hand, a growing scholarship has shown that there are important reasons why full input disclosure may be undesirable and unfeasible not least due to the counter-part obligations and merits of confidentiality, privacy and anonymity.

In the final section, a brief discussion on the overriding transparency goal of building public trust in risk regulation was provided. Although there are many goals of transparency that are relevant to multiple different forms, the goal of building public trust has been prominent in risk regulation. The review illuminated that there are both optimistic and pessimistic arguments relating to the effects of transparency on trust but also that there has been a distinct lack of empirical research beyond policy experiments.

Overall, perhaps the most important outcome from this literature review chapter is the finding that the large majority of debate on different forms of transparency has relied on anecdotal evidence and theoretical reasoning. Much of the literature has also been confused and decontextualized from its regulatory context and real world setting primarily due to the ambiguity of transparency. This is especially true with regards to input transparency policies. What is needed now is more empirical studies on input transparency policies in particular, that are not divorced from their real world context.

Chapter IV: METHODOLOGY

> *"Given the high value put on transparency, its ideological currency, and scholarly interest, it is surprising to find that there are few empirical studies of the effects of transparency. […]. There continues to be a dearth of studies empirically testing the theoretical claims of transparency advocates, even as legislation and institutional support for their case accumulates exponentially"* (Etzioni, 2010: 6).

This chapter provides a detailed explanation of the methodology adopted in this thesis. This centres on the use of a case study to empirically examine the effectiveness of EMA's transparency policies (Chapter I). A variety of approaches could be chosen for examining the phenomenon of transparency in risk regulation (Coglianese, 2012). These include case studies but also controlled and randomised experiments, observational studies (quasi-experiments), histories, field studies, and ethnographies (Yin, 2009; Coglianese, 2012). Although there has been a dearth of empirical research historically (Chapter III), the most popular approach has been to use nominal measures (e.g. to create an index or proxy of some sort) (Heald, 2006) or more recently to conduct policy experiments (Grimmelikhuijsen, 2010; De Fine Licht *et al*. 2014; Löfstedt and Way, 2016a, 2016b; Cucciniello *et al*. 2017). However, there is no single 'right way' of conducting social science research (Martin and Flowerdew, 2005). Different quantitative and qualitative methodologies inevitably have their own strengths and weaknesses. Thus it is essential to openly acknowledge and explain the strengths and weaknesses of the methodology chosen in this thesis.

The chapter is structured as follows. The first section explains what case studies are and how they can be differentiated from other empirical inquiries. It also explains why three critical conditions for conducting case studies are applicable to and appropriate for this thesis. These are (1) the type of research question chosen; (2) the inability of the investigator to control behavioural events; and (3) the study's focus on contemporary rather than historical events (Yin, 2009: 8). The second section addresses two main criticisms of case study research. It subsequently emphasises the need to develop a systematic and detailed research design. The third section explains that this study uses an overall explanatory case study design with a preliminary exploratory stage. The study is also a single case of the EMA's transparency policies with three embedded sub-units of analysis. The four main data collection methods are then explained and justified. These are extensive historical and contemporary documentation (including archival analysis); direct observations and interviews at 18 elite multi-actor policy

meetings; and surveys of patients (N=1,010) and medical doctors (N=1,005). An extended explanation of how and why surveys were embedded into the case study design is provided primarily because there remains debate over the use of surveys in case study research (Gable, 1994; Robson and McCartan, 2016). The fourth section explains how the case study data is analysed and presented in order to directly address the research question and hence evaluate EMA's transparency policies and contribute to the broader transparency literature. This is followed by a concluding discussion on the study's limitations.

(4.1) The case study approach

Case studies are widely used in the social sciences and have been for a long time (*see* Hemel, 1992; Gillham, 2000). This includes investigations related to 'transparency' (e.g. Moon, 2003; Bijker *et al*. 2009; Coglianese, 2012). In this thesis, a case study is defined as "a strategy for doing research which involves an empirical investigation of a particular contemporary phenomenon within its real-life context using multiple sources of evidence" (Robson and McCartan, 2016: 150). This means that a case study is not a method but can be used as "a stance or approach" for conducting empirical research on the concept of transparency (Robson and McCartan, 2016: 150). According to Yin (2009: 18), case studies have two specific definitional components. The first is that:

> *"[A case study] investigates a contemporary phenomenon in depth and within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident"* (Yin, 2009: 18).

This means that case studies have the advantage of enabling the researcher to investigate the contemporary phenomenon of transparency, which exists "in the here and now" (Gillham, 2000: 1; Gibbert *et al*. 2008: 1466). In contrast, histories are unable to do so as they provide evidence about non-contemporary phenomena (Yin, 2009; Crow and Edwards, 2012). Case studies also have the advantage of enabling the researcher to investigate the phenomenon of transparency in its real-life context and so when "important contextual conditions" need to be considered (Yin, 2009: 18; Yin and Davis, 2007). They cannot be conducted devoid of their context (Miles *et al*. 2014) and, as Flyvberg (2006: 236) argues, "the most advanced form of understanding is achieved when researchers place themselves within the context being studied". They are especially useful when "the boundaries between phenomenon and context

are not clearly evident" (Yin, 2009). In other words, case studies are particularly useful in this case as it is difficult to draw precise boundaries between the phenomenon of transparency and the context in which it is found (Gillham, 2000). In contrast, a weakness of experiments is that they deliberately divorce the phenomenon of transparency from its real-life context typically by 'controlling' for certain contextual conditions (e.g. Grimmelikhuijsen, 2010, 2012; De Fine Licht *et al*. 2014) (Yin, 2009).

The second definitional component of case studies centres on how data is collected and analysed (Gilham, 2010; Robson and McCartan, 2016). As Yin (2009: 18) explains:

> *"…because phenomenon and context are not always distinguishable in real-life situations, other technical characteristics, including data collection and data analysis strategies now become the second technical definition of case studies".*

Case studies draw on "multiple sources of evidence" that each have their relative advantages and disadvantages (Gilham, 2010; Robson and McCartan, 2016). This is because they cope "with the technically distinctive situation in which there will be many more variables of interest than data points" (Yin, 2009: 18; Yin, 1994). Therefore they enable the phenomenon of transparency to be studied through multiple lenses (Baxter and Jack, 2008). As a result, they rely on multiple sources of evidence that benefit from the prior development of theoretical propositions for collecting and analysing data (Yin, 2009: 18). This means that one source of evidence is unlikely to be sufficient (or sufficiently valid) in this case study (Gilham, 2010). Furthermore, it is now widely accepted that that both qualitative and quantitative methods can be used in case study research (Gerring, 2006), although "qualitative data are almost invariably collected" (Robson and McCartan, 2016: 149).

Beyond this two-part definition, three critical conditions are required for adopting a case study (Yin, 2009: 8), all three of which are relevant to this thesis on transparency in risk regulation. The first critical condition centres on the type of research question being posed (Yin, 2009). There are various ways of categorising research questions that can be linked to specific empirical enquiries (Hendrick, 1993; Blaikie, 2007: 6-7). One common and well-known categorisation distinguishes between 'who', 'what', 'where', 'how' and 'why' type questions. In the transparency literature (Chapter II), investigators have often chosen 'how many' and 'how much' type questions. For example, some of the most common questions have centred

on the quantity of documents an organisation has released (or not) as a measure of 'transparency' (e.g. Alt and Lassen, 1999; Doshi and Jefferson, 2013b, 2016). In contrast, this thesis seeks to answer a 'how' type question (Chapter I). The study seeks to understand how effective EMA's transparency policies have been in achieving the agency's objectives. Case studies (as well as histories and experiments) are particularly appropriate for answering such 'how' (and 'why') questions (Stake, 2005; Yin, 2009). According to Yin (2009: 9), this is because these questions "deal with operational links needing to be traced over time, rather than mere frequencies or incidents". It is therefore appropriate to use a case study in this thesis because the research question being asked is a 'how' question rather than, for example, a 'what', 'when' or 'how many' type question.

The second critical condition concerns the extent of control the investigator has over actual behavioural events for answering the research question (Yin, 2009). Experiments have become an increasingly popular method for examining what effects 'transparency' has on different public policy objectives such as trust (e.g. Grimmelikhuijsen, 2012), legitimacy (e.g. De Fine Licht *et al*. 2014) or empowering citizens (e.g. Löfstedt and Way, 2016a; 2016b). One main strength of such experiments is that they can measure causality and hence the effects of one variable on another. Yet, at the same time these experiments involve deliberately "divorcing" the phenomenon of transparency from its real-world context (Yin, 2009) thus reducing real-world validity (Robson and McCartan, 2016). In other words, experiments seek to assess whether an effect actually exists and have a high level of rigour and control but do not mirror real life situations (Grimmelikhuijsen, 2012). In contrast, case studies have the advantage of enabling the researcher to examine transparency policies "when the relevant behaviours cannot be manipulated" (Yin, 2009: 11). For measuring how effective EMA's transparency policies are in achieving the agency's objectives, it is not possible for the investigator to manipulate behaviours without divorcing those behaviours from their real-life context. Thus it is appropriate to use a case study in this thesis because the investigator does not have control over actual behavioural events that are needed to answer the research question.

The third critical condition concerns the degree of focus on contemporary as opposed to historical events. Histories are most useful for looking at past events where "no relevant persons are alive to report, even retrospectively, what occurred and when the researcher must rely on primary and secondary documents as well as artefacts" (Yin, 2009: 11). Several

transparency scholars have adopted such approaches for analysing transparency over time (Hood, 2006a; Meijer, 2015; Way and Löfstedt, forthcoming). For example, Meijer (2015) conducted an historical analysis of government transparency in the Netherlands over the past 250 years. Case study designs can include, and often do include, histories as one of several data collection methods. However, they also include techniques that go beyond historical data through collecting contemporary evidence (e.g. observations or interviews) (Yin, 2009). This is important because, although historical context is essential, this thesis focuses on examining the *current* policies initiated by the EMA and the *current* perspectives of multiple actors living in the here and now. It is therefore appropriate to use a case study because the primary focus of this thesis is on the effectiveness of contemporary transparency policies as opposed to historical events.

(4.2) Traditional prejudices

Case studies have not always been as widely used and accepted in social science research as they are now (David, 2005; Yin, 2013; Robson and McCartan, 2016). They have traditionally received a great deal of criticism. For example, in a strongly worded paper, Campbell and Stanley (1966: 6-7) stated that "such studies have such a total absence of control as to be of almost no scientific value". However, many critics, including Campbell (1975), have since become great advocates of case study research (Flyvberg, 2006). These authors have primarily argued that the approach has been misunderstood or simply used incorrectly (Flyvberg, 2006; Robson and McCartan, 2016), which some authors now describe as 'traditional prejudices' (e.g. Yin, 2009). In seeking to avoid common pitfalls in conducting case study research, two of the most persistent prejudices are addressed here.

One traditional prejudice against case studies centres on their apparent 'non-generalisability' (Yin, 2009; Gilham, 2010). Flyvberg (2006) summarises this criticism as follows: "One cannot generalise on the basis of a single case therefore the case study cannot contribute to scientific development". In other words, several authors have argued that one cannot generalise from a single case rendering the research approach as non-scientific. While some critics have argued that case studies should only be used for pilot studies (e.g. Abercrombie *et al*. 1984), others have strongly argued that their non-generalisability presents a devastating blow and renders case study research almost useless (Campbell and Stanley, 1966; Diamond, 1996: 6).

However, these arguments are misleading (*see* Flyvberg, 2006 for a detailed discussion). One main argument is that the generalisability of a case study depends on what case one is referring to. For example, by taking Karl Popper's logic of 'falsification', one can quickly see that a study identifying even a single case of *one* black swan can falsify the assumption that all swans are white (Flyvberg, 2006). A second argument is that case studies are not generalizable *statistically* but they are generalizable *analytically* (Yin, 2009). As Yin (2009), concisely puts it: "The short answer is that case studies, like experiments, are generalizable to theoretical propositions and not to populations or universes". They seek to expand and generalise theories (analytic generalisation) but they do not seek to enumerate frequencies (statistical generalisation) (Yin, 2009). Therefore a key argument is that generalisability should not be confined to sampling and statistical significance (i.e. statistical generalisation) in social science research (Donmoyer, 2000).

A second traditional prejudice towards case studies is their apparent lack of rigour (Campbell, 1975; Daft and Lewin, 1990; March *et al.* 1991; Irani *et al*. 1999). Some authors have argued that case studies have methodological flaws including being too subjective and giving too much scope for the researcher's own interpretations (Diamond, 1996; Hyett *et al*. 2014). These authors often argue that there is "a bias towards verification, that is, the tendency to confirm the researcher's preconceived notions" (Flyvberg, 2006: 221). Therefore case studies have been criticised for not applying scientific methods that seek to curb out "one's tendencies to stamp one's pre-existing interpretations on data as they accumulate" (Diamond, 1996 In: Flyvberg, 1996: 234). Some critics go further and argue that case studies are too often conducted in a sloppy fashion, unsystematically or even dishonestly (e.g. Bromley, 1986).

However, these traditional prejudices against case studies have in themselves been criticised (Flyvberg, 1991: 137-138). One argument is that case study *research* should not be conflated with case study *teaching* (*see* Garvin, 2003). Yin (2009) clarifies that case study teaching 'devices' deliberately alter case study materials to emphasize a particular point. In contrast, case study research forbids doing so and requires that empirical data is rigorously and fairly presented (Yin, 2009: 14). A second argument is that bias, dishonesty, and subjectivity can be introduced into almost any research design and is not unique to case study research. This includes historical research (Crow and Edwards, 2012), experiments (e.g. interpreter bias)

(Rosenthal, 1996, 2009), surveys (Fowler, 2013), and others (*see* e.g. Podsakoff *et al*. 2012). For example, one of the main arguments against case studies – bias towards self-verification – exists and applies to all methods (Flyvberg, 2006). Some have gone further by arguing that case studies actually contain a greater bias towards falsification than bias towards verifying pre-conceived notions directed by the investigator (e.g. Flyvberg, 2006: 237). Thus it is widely agreed that case studies are no less rigorous than any other research method and criticisms are "misguided" (Campbell, 1975: 225).

These criticisms highlight the need to create a systematic and detailed case study research design. Such a research design can provide a blueprint detailing "what questions to study, what data are relevant, what data to collect, and how to analyse the results" (Yin, 2009: 26). Indeed, many different designs could have been chosen for empirically examining the concept of transparency in risk regulation. The specific design adopted in this thesis is where this chapter turns next.

(4.3) Choosing the EMA case

A *single* case study design of the EMA and its transparency policies was chosen for this study. The boundaries of the case are defined by (1) the time period of January 1995 (when the agency was established) to December 2016 (shortly before this thesis was finalised) and (2) the agency's transparency policies that were introduced (or proposed to be introduced) during that period. Therefore the case study excludes other agency activities not related to transparency. 'Transparency policies' are defined and categorised using the typology developed in Chapter II and so include the full range of transparency objects, mechanisms, goals and audiences. Four main reasons why EMA was chosen were explained in the introductory chapter and are not repeated here (*see* section 1.3). Rather, this section provides a more detailed understanding of the research design.

Single cases can be distinguished from multi-case designs (e.g. comparing EMA with other decentralised EU agencies). One main reason for limiting the study to a single case is that it would not have been possible to examine the concept of transparency in as much depth if multiple cases were chosen and compared. The investigator was constrained by resources including being the only case study investigator and having a fixed time limit to collect and

analyse data. Transparency is also a relatively new concept of interest in risk regulation and conducting a substantial amount of prior exploratory work was resource intensive. With that said, future empirical enquiries can use the typology (Chapter II), literature review (Chapter III), and study findings (Chapter V-IX) to compare the EMA case with other regulatory authorities responsible for risks to human health and the environment.

EMA can also be considered as a 'typical' single case (or what is sometimes known as the 'representative' case), which can be distinguished from those categorised as critical, extreme, revelatory, or longitudinal (Yin, 2009: 47-50). EMA is 'typical' of a regulatory authority responsible for risks to human health and/or the environment that has introduced many policies designed to enhance the transparency of its scientific and non-scientific activities. For example, similar to numerous other regulatory authorities (e.g. other EU decentralised agencies, FDA and Health Canada), EMA have introduced the full range of transparency policies that seek to make both decision-making events and processes (i.e. inputs, processes, and outputs) more visible to outsiders (Chapter V). This is not to say that EMA does not have unique characteristics including with regard to transparency (e.g. regulating pharmaceuticals, its organisational structure, its specific responsibilities etc.). Rather, the agency is typical of the numerous risk regulation organisations that have strongly committed to enhancing transparency by introducing a range of policies.

(4.4) Explanatory case design

The case study had an explanatory design for examining the effectiveness of EMA's transparency policies[16]. Explanatory cases can be used "to explain causal relationships and to develop theory" (Mills *et al*. 2010: 370) and so was appropriate for answering this study's research question:

> *How effective have the European Medicines Agency's input transparency policies been in achieving its public policy objectives?*

[16] All investigations were carried out in accordance with King's College London rules on ethical approval (REP/13/14-100).

However, before the main explanatory case study was conducted, a preliminary exploratory study of the EMA's transparency policies was necessarily undertaken. In other words, the exploratory case served as a preliminary step in the overall explanatory case study design (*see* Robson and McCatan, 2016: 61). To be clear, although the exploratory case started in October 2012, the EMA's transparency policies were continually 'explored' throughout the data collection period as new policies were proposed and introduced by the agency. The main overriding reason for conducting a preliminary exploration was that there has been a distinct lack of sophisticated research on transparency either on EMA or in the pharmaceutical domain. This is especially true when compared with the environmental policy context (e.g. Gupta and Mason, 2014). This meant that few clearly formulated hypotheses of transparency in pharmaceutical regulation could be tested without initially exploring and understanding EMA's policies.

The first main objective of the preliminary study was to identify and distinguish between EMA's transparency policies and subsequently categorise them according to the (emerging) typology of transparency in risk regulation (Chapter II). Although EMA has introduced many policies, few policymakers or academics have clearly distinguished between different types. The exploratory study provided a clear understanding of EMA's past and developing policies including *what* aspects of risk regulation EMA seeks to make more transparent (i.e. objects), *how* (i.e. mechanisms), *why* (i.e. goals/reasons), and for *whom* (i.e. audiences). The exploratory study also provided an essential historical context for the agency's contemporary policies. Although the case study research started in October 2012, EMA introduced many transparency policies since its establishment in 1995. Thus in order to examine the effectiveness of EMA's policies it was essential to first place them in historical context.

The second main objective was to formulate a more precise research question (Chapter 1) (Mills *et al*. 2010). Case studies seek to answer specific questions and "framing good questions is the most important part of the research procedure" (Gillham, 2000). However, the research question was fairly loose to begin with in this study, which is not uncommon in case study research (Gillham, 2000). A relatively new field of scientific investigation was studied in this thesis – the effectiveness of transparency in risk regulation – in which few real-life empirical research questions have been addressed (Etzioni, 2010) (Chapter III). Therefore conducting an

exploratory study was essential for this study because the research question could not be clearly formulated without doing so (Mills *et al.* 2010).

After these two objectives had been achieved, the main explanatory component of the study commenced in mid-2013. The main EMA case had three embedded sub-units of analysis (Yin, 2009). These provided the necessary depth of analysis for answering the main research question and as Baxter and Jack (2008) comment: "The ability to engage in such rich analysis only serves to better illuminate the case". Conducting an alternative holistic approach would have been inappropriate (Yin, 2009). Such a study would not have provided the necessary level of detail required for empirically examining the effectiveness of EMA's transparency policies. For example, examining all policies holistically would have blurred important distinctions between different types introduced by the agency.

The three embedded sub-units of analysis were EMA's three main input transparency policies (Chapter VI):

- Sub-unit 1: EMA's online clinical trials register called EU-CTR (clinicaltrialsregister.eu)
- Sub-unit 2: Publishing summary-level clinical trial results on EU-CTR
- Sub-unit 3: Publishing clinical study reports online (clinicaldata.ema.europa.eu)

These three policies were chosen as sub-units of analysis for three main reasons. First, they all seek to enhance the transparency of the information that underpins decision-making in EMA's scientific committees. In other words, they can be categorised as EMA's main 'input' transparency policies (Chapter II). The literature review showed that such input policies have received some of the least empirical attention (Chapter III). In contrast, output policies – and, to a lesser extent, process policies – have received some of the most empirical attention[17]. Thus investigating input transparency policies promised to contribute significantly to the emerging literature (Chapter III).

Second, all three input policies were either introduced or revised during the study period. For example, in November 2012, EMA's 3rd Executive Director, Guido Rasi, announced that the

[17] Although it is worth noting that most output policies can be categorised as risk communication studies in the fragmented literature rather than transparency policy studies *per se.*

agency would be committed to developing new transparency policies for proactively publishing input data online:

> *"Today represents the first step in delivering our vision. We are not here to decide if we will publish clinical-trial data, only how. We need to do this in order to rebuild trust and confidence in the whole system."* (EMA, 2012a).

This meant that, from the very beginning of the case study period, there was a unique opportunity to follow and examine the evolution of EMA's input policies in real time. This includes following the key transparency policy materials, people, and events (*see* Wood, 2016). EMA also received substantial external pressure to introduce new input policies between 2010 and 2016 (Chapter VI). This meant that discussing the effectiveness of these three policies with key actors and audiences was highly topical and hence complemented data collection.

Third, the three embedded sub-units provided a mixture of input policies that can be compared and contrasted. Each policy seeks to make different levels of clinical trial data more transparent (Chapter VI). Each policy also seeks to make input data more transparent for various audiences ranging from patients and doctors to external researchers and other regulatory bodies, as well as industry. Multiple levels of analysis on EMA's input policies could therefore be made in order to address the research question comprehensively. This includes "within the sub-units separately (within case analysis), between the different sub-units (between case analysis), [and] across all the subunits (cross-case analysis)" (Baxter and Jack, 2008: 550).

After the three sub-units had been identified, the evolving typology of transparency in risk regulation was applied to EMA's three input policies (Chapter II). Making clear distinctions was essential for examining the effectiveness of each input policy and hence answering the research question. For example, examining how effective EMA's clinical trial register (sub-unit 1) has been in achieving the regulators' policy objectives requires understanding: what data and information EMA's register seeks to make more transparent (i.e. the target objects of the policy) and how (i.e. the expected mechanisms of the policy); what the regulators seek to achieve with its clinical trial register (i.e. the intended goals of the policy); and who the register is intended to be used by or benefit (i.e. the target audiences of the policy). Although all three policies can broadly be defined as 'input' transparency policies, they each have slightly different characteristics and purposes.

The next stage of the explanatory case study was to collect data and evidence on the effectiveness of EMA's input policies. As explained in the introductory chapter (Section 1.2), measuring effectiveness requires measuring whether the audiences of EMA's policies can receive, process, digest and use the information made publicly available online (Heald, 2006). This means that, in order to answer the research question, case study evidence needed to be collected on the experiences of the *audiences* of EMA's policies (i.e. those that are expected to receive, process, digest and use the information uploaded online). These audiences of EMA's policies were usefully categorised into six main groups (Table 4.1).

Table 4.1: EMA's transparency policy audiences categorised into six main groups

	Audiences of EMA's policies	**Examples**
Group 1	External 'independent' scientists	Clinical trialists, data miners and systematic reviewers (e.g. the Cochrane Collaboration or University academics)
Group 2	Industry	Trade bodies (e.g. EFPIA[18] or ABPI[19]), pharmaceutical companies (e.g. GlaxoSmithKline, Merck, Pfizer)
Group 3	Non-EMA regulators	Regulators from NCA (e.g. MHRA or AEMPS) and non-EU regulatory authorities (e.g. FDA, Swissmedic, Health Canada)
Group 4	Policy and healthcare decision-makers	Government committee members and health technology assessors (e.g. the UK National Institute for Healthcare Excellence [NICE] or the Germany Agency for Health Technology Assessment [DAHTA])
Group 5	Medical doctors	Doctor advocacy groups, general practitioners, specialist doctors.
Group 6	Patients	Patient and consumer advocacy groups, individuals with medical conditions, the general public.

One notable challenge with collecting evidence from EMA's transparency audiences was that there are millions of individuals, groups and institutions across the world that are either directly (i.e. accessing EMA's web-portals) or indirectly (i.e. through intermediaries) expected to receive, process, digest, and use the data made publicly available. This meant that it was not possible to collect in-depth case study evidence on EMA's policies *directly* from all audiences (i.e. directly from those millions of individuals, groups, and institutions). Doing so would have

[18] European Federation of Pharmaceutical Industries and Associations
[19] Association of the British Pharmaceutical Industry

been an enormous resource-intensive undertaking that would, for example, necessarily involve collecting intensive and extensive qualitative and quantitative data on a substantial international scale. In order to overcome this challenge, the investigator adopted two main approaches.

The first approach was to collect substantial case study evidence from the perspectives of the most knowledgeable elite experts that *represent* the main audiences of EMA's transparency policies (Table 4.1). This was primarily achieved using three research methods: documentation, observations, and interviews (*see* sections 4.5 and 4.6). To be clear, these elite experts represent the millions of individuals, institutions, and groups that are expected to use the data made publicly available by EMA either directly or indirectly. They have a sophisticated and knowledgeable understanding of the perspectives and experiences of the audiences of EMA's policies. For example, senior representatives from the European Federation of Pharmaceutical Industries and Associations (EFPIA), a Brussels-based trade association representing industry, have extensive in-depth knowledge about the perspectives of pharmaceutical companies (Group 2 in Table 4.1). In comparison, senior regulators from national competent authorities (NCAs) (e.g. the UK Medicines and Healthcare products Regulatory Authority [MHRA]) and non-EU regulatory authorities (e.g. the US FDA or Health Canada) have extensive knowledge on the perspectives of non-EMA regulators (Group 3 in Table 4.1). Elite expert representatives were therefore considered highly appropriate and useful sources for gathering evidence on the experiences and perspectives of the six main audiences of EMA's policies.

The second approach was to collect further evidence on the effectiveness of EMA's policies directly from (1) patients and (2) medical doctors (i.e. Groups 5 and 6 in Table 4.1). Put another way the investigator chose to commit resources to collecting further evidence on these two groups directly and hence to complement evidence collected using the first approach. There were two main reasons why further evidence was collected from these two groups, that is, over any other transparency audience (Table 4.1). First, patients and doctors are one of the most important audiences of EMA's transparency policies. They are at the coal-face of decision-making over medicines. Therefore the effectiveness of EMA's transparency policies is highly dependent on these two groups. Second, only limited evidence could be collected on the perspectives of patients and doctors using the first approach. In contrast, substantial quantities of evidence could be collected on other audiences of EMA's policies through the first approach.

For example, most documentation evidencing the effectiveness of EMA's transparency policies – such as scientific journal articles, interview transcripts, public consultations (section 4.5) – has focused on the perspectives of external researchers that intend to re-use data made publicly available (e.g. Doshi and Jefferson, 2013a, 2013b, 2016). Therefore there was limited case study evidence that could be collected on the perspectives of two of the most important audiences of EMA's transparency policies and so further data was necessarily collected.

The main method adopted for obtaining further evidence on the perspectives of patients and doctors was surveys (*see* section 4.7), which was complemented with documentation, observations, and interviews (e.g. through patient advocacy group representatives) (sections 4.5-4.6). Surveys are not typically included in case study designs and so it is important to clarify how they were used in this study (Gable, 1994; Robson and McCartan, 2016). The survey research method seeks to make statistical generalisations whereby an "inference is made about a population (or universe) on the basis of empirical data collected about a sample from that universe" (Yin, 2009: 38). In this study, surveys were used to make such inferences from two representative samples of patients and doctors (*see* section 4.6.1). One goal of conducting these surveys was therefore to make statistical generalisations about the opinions and perspectives of patients and doctors, two under-represented audiences of EMA's policies (Table 4.1).

In turn, the overriding purpose of conducting surveys was to generate data on patients and doctors that could contribute towards the pool of evidence on the main EMA case. This means that although statistical generalisations were, indeed, made about patients and doctors, the survey method did <u>not</u> seek to create statistical generalisations about the overall EMA case. Rather, this case study sought to create analytic generalisations (Gomm *et al*. 2000; Yin, 2009). This is important because, as Yin (2009) explains: "a fatal flaw in doing case studies is to conceive of statistical generalisation as the method of generalising your case study results". Thus the surveys were primarily considered as a fourth research method adopted in this mixed multi-methods case study that could be used to generate and collect data on the perspectives of patients and doctors.

Furthermore, the surveys specifically generated data on the perspectives of patients and doctors receiving benefit-risk and other regulatory information made available by EMA through its transparency policies. In particular, the investigator collected evidence on where patients and

medical doctors obtain medicines information and which ones they trust; how familiar they are with the regulators; how they might react to receiving safety-related information; and other evidence. These questions are important because information is hypothesised to play a central "mediating role" (see Grimmelikhuijsen, 2010: 16) in achieving EMA's transparency policy objectives for patients and doctors (EMA, 2014a, 2014b). For example, by making input data publicly available patients and doctors are expected to (directly or indirectly) receive, process, digest, and use such information in order to complement fully-informed decision-making. Indeed, the central policy mechanism for achieving transparency is the provision of more information about a whole range of scientific and non-scientific agency activities. Hence questions such as where patients obtain medicines information, what sources they trust, how they typically react to receiving information that points to safety issues and how well they understand the scientific medicines evaluation system were all considered important in understanding the effectiveness of EMA's policies.

(4.5) Documentation

The first main data collection method can be categorised as documentation, which, according to Yin (2009), should be included in almost every case study design. A comprehensive range of documents was collected and analysed in order to minimise bias and corroborate evidence from multiple sources in-depth (Yin, 2009). All documents related either directly or indirectly to EMA's transparency policies (and their audiences) that were introduced between January 1995 and December 2016. This includes some documents that date as far back as the mid-1960s that indirectly relate to the evolution of transparency in pharmaceutical regulation and hence provide essential background for the agency's contemporary policies (e.g. Directive 65/65/EEC). A wide variety of official and non-official documents were collected that provide evidence on EMA's policies from the perspectives of EMA's transparency audiences (Table 4.1). While some documents were collected during the initial exploratory phase of the research, others were continually collected as and when they became available in what Wood (2016) categorises as "following the policy materials". Therefore many important sources of evidence were used for understanding the agency's policies before the case study commenced (1995-2012) and for following the development of those policies thereafter (2012-2016).

One particularly important source was EMA's official annual reports spanning from 1995 to 2016 (e.g. EMA, 2004). Similar to other decentralised EU agencies, EMA is required to submit informative and official reports on its activities to the European Commission annually (EMA, 2017e). Amongst other activities, they contain perspective pieces on the agency's yearly developments from the two most senior regulators, the Chair of the Management Board and the Executive Director, which for 1995-2016 almost always included reflections on transparency. They also provided a clear annual update on the main changes to the agency's transparency policies. Notably, in every single report and without exception the regulators discussed EMA's progress on transparency and often with dedicated sections.

Policy documents were a second particularly important source of documentation. Such documents, published by EMA, detailed the purpose, scope and objectives of every EMA policy. Draft versions were also used (e.g. EMA, 2009; EMA, 2013a). For example, EMA's October 2014 clinical study reports transparency policy (EMA, 2014b) was initially released in draft form for public consultation in June 2013 (EMA, 2013a). By comparing the 2013 draft version with the final 2014 policy, significant changes to EMA's transparency strategy could be identified and evidenced. Policy documents published by other organisations were also used. This includes the EFPIA and the Pharmaceutical Research and Manufacturers of America's (PhRMA) joint policy document '*Principles for Responsible Clinical Trial Data Sharing*' (EFPIA-PhRMA, 2014), as well as numerous transparency policy documents published by national pharmaceutical authorities.

One source of evidence, closely related to EMA's policy documents, were comments from public consultations. Similar to all other decentralised EU agencies, EMA frequently consults its many stakeholders on new policies. Public consultations can produce substantial quantities of evidence on EMA's policies from the perspective of different audiences. For example, in three months alone EMA received over 1,000 comments from over 160 individuals and organisations on its 2013 draft clinical trial data transparency policy (i.e. evidence relating to sub-units 3 and 4) (EMA, 2014c). Detailed comments were given by many audiences including representatives from pharmaceutical companies and trade bodies, NCAs, patient and doctor advocacy groups, medical journal editors, campaign groups and the wider medical community. Indeed, all three input polices, that make up the case study sub-units of analysis, received extensive comments.

Furthermore, many other types of documentation produced by EMA was used as case study evidence. This includes management board meeting minutes and agendas (EMA, 2017f), letters and correspondence (Pott, 2015), workshop reports (EMA, 1997a, 2012a), and a multiplicity of documents published on EMA's website (ema.europa.eu). For example, the European ombudsman and EMA management board publicly exchanged several lengthy and highly informative letters on EMA's transparency policies during the study period (O'Reilly, 2013; Pott, 2015).

Another highly important source of documentation was scientific journals (including journal archives). These official information channels have been one of the main forums for discussing EMA's transparency policies in the pharmaceutical policy domain. This ranges from scientific medical journals (e.g. the *Lancet*, *New England Journal of Medicine*, *British Medical Journal*, *Annals of Internal Medicine*, *Journal of the American Medical Associations*), to more generalised scientific journals (e.g. *Nature, Science*). Journal articles have included detailed perspectives and opinion pieces on EMA's policies from a remarkable array of senior and influential actors, as well as the wider medical community (e.g. journal editors, patient and doctor advocacy groups, influential opinion leaders, systematic reviewers, etc.). While the majority of articles on EMA's policies were published after 2010 (and after the agency significantly changed its transparency strategy), many were also published before 2010 including commentaries on EMA's earliest pioneering policies (e.g. Abbasi and Herxheimer, 1998). Some medical journal editors have also actively campaigned and lobbied the EMA in seeking to influence the agency's policy decisions and, in so doing, produced numerous documents. For example, one of the *British Medical Journal*'s ongoing campaigns has been to pressurise EMA into publishing clinical trial data (*see* BMJ, 2017).

Since 2007, EMA regulators have increasingly communicated their policy opinions and perspectives on transparency in medical journals (e.g. Eichler *et al*. 2012, 2013; Bonini *et al*. 2014), which some regulators view as a highly useful communication channel (personal communication, 2015). For example, in December 2014 Sergio Bonini and other senior EMA regulators provided an agency perspective article on the sharing of clinical trial data (i.e. evidence relating to sub-units 1-4) (Bonini *et al.* 2014). The regulators have also given informative interviews that have been reported in full in several scientific journals. For example, *Nature Reviews Drug Discovery* interviewed EMA's 2nd Executive Director, Thomas

Lönngren , in 2010 (Mullard, 2010) and *Nature Medicine* interviewed EMA's 3rd Executive Director, Guido Rasi, in 2012 (Looney, 2012).

Beyond scientific journals, many perspectives on EMA's policies have been documented in books. Some of the most highly influential were detailed in pop science books such as Ben Goldacre's (2008) '*Bad Pharma: How Medicine is Broken and How We Can Fix It*'. Other notable books were also written by senior medical journal editors such as the past editor-in-chief of the *New England Journal of Medicine* (Angell, 2004) and the past editor of the *British Medical Journal* (Smith, 2010). Other books were written by academics, which provide a range of views and evidence on EMA's policies (e.g. Abraham and Lewis, 2000; Permanand, 2006; Avorn, 2008; Demortain, 2011). Several organisations have also published books or lengthy reports on transparency in the pharmaceutical domain. This included the House of Commons Science and Technology Committee's '*Clinical Trials*' report (Science and technology Committee, 2013) and the Institute of Medicine's '*Sharing Clinical Trial Data: Maximising Benefits, Minimizing Risk*' report (Institute of Medicine, 2015).

Many journalists have also reported extensively on EMA's transparency policies. The investigator followed numerous online news outlets during the study period including *MedScape, Regulatory Focus, BioCentury, Genetic Engineering and Biotechnology News, Drug Store News, InPharma.com, FierceBiotech, FDA news*, and others. These outlets provided a rich source of information on EMA's evolving policies and enabled the investigator to stay up-to-date with important policy developments. Some news articles also included interviews with notable policy actors such as *ChemistryWorld* or *PharmaBoardRoom* interviewing Guido Rasi about the agency's evolving transparency policies. Several online pharmaceutical magazines also provided further sources of evidence. This includes *the Economist*, the Drug Information Association's magazine, '*Global Forum*', and *PharmaTimes* (the UK's leading pharmaceutical magazine). Furthermore, news clippings from several broadsheet newspapers were continually collected throughout the research period. For example, clippings from prominent *Financial Times* journalists, Andrew Jack and Andrew Ward, were collected frequently.

Some documents were harder to retrieve, yet, provided important case study evidence. First, some materials were obtained by proactively requesting them directly from EMA or NCA

regulators (e.g. Egger, 2011). Second, some materials were only found after searching deep into library archives (e.g. Sauer, 1997). Third, EMA's 1st Executive Director, Fernand Sauer, has many unpublished manuscripts that are only available on his website such as '*Institutionalising European Agencies: An Insider Perspective*' (Sauer, 2009). Fourth, some publications were harder to retrieve because they are out of print. For example, it took several months to obtain a copy of EMA's '*Celebrating 10 Years: Portrait of the European Medicines Agency*' book (EMA, 2005a) that includes detailed information on the views of different actors from EMA's establishment up until 2005. Furthermore, some documents were only made available at policy events attended by the investigator in person.

(4.6) Observations and interviews

In order to conduct the next two data collection methods, observations and interviews, the investigator attended a total of 18 elite policy meetings in person between November 2012 and December 2016[20]. The meetings provided numerous opportunities to collect highly relevant evidence from many transparency audiences over a total of 23 days (Table 4.1). This included opportunities to conduct observations and interviews with all elite actors representing all seven audiences of EMA's transparency policies. In particular, the meetings were attended by some of the most senior European pharmaceutical policy actors and experts, representing almost all transparency audiences, ranging from NCA regulators and patient advocacy groups, to trade bodies and industry, as well as the wider medical community (e.g. journal editors, data miners, influential opinion leaders). Notably, attending a variety of meetings was an important strategy as it provided multiple and differing opportunities to collect data. The meetings also enabled the investigator to examine the evolution of the regulators' policies by, as Wood (2016) puts it, "following the policy people and meetings" throughout the case study period.

The 18 elite policy meetings, attended in person by the investigator, can be categorised into four types. First, seven meetings were public events attended by the investigator either on request or by invitation from regulators at EMA or NCAs (hereafter, 'Type 1' meetings). The meetings were attended by 40 to over 100 delegates who collectively represented all policy

[20] In addition to the 18 meetings attended in person, numerous meetings were also observed on live web-streams. Although this additional approach was helpful when the investigator was unable to attend in person (e.g. due to budget restraints or timing issues), it had limitations such as the investigator being unable to gather evidence from attendees in person. Therefore these meeting are not discussed in detail. Rather, they contributed to the extensive documentation collected.

actors and most audiences of EMA's policies. They were held at EMA's headquarters, NCAs, or independent venues and lasted between one and two days (Table 4.2).

Table 4.2: Dates, locations and attendees of Type 1 meetings.

Date	Location	Attendees
Nov 2012	EMA headquarters (London, UK)	Over 100 of the most elite actors representing all audiences of transparency (EMA, 2012a).
Feb 2013	Conway Hall Ethical Society (London, UK)	Over 100 delegates representing all audiences of transparency, the general public.
July 2014	MHRA (London, UK)	Over 45 senior and junior MHRA regulators
Sept 2014	DKMA[21] (Copenhagen, Denmark)	Over 40 senior and junior DKMA regulators
Dec 2015	Royal College of Physicians (Edinburgh, Scotland)	Over 40 of the most elite representatives from NCAs and EMA including many heads of departments
Mar 2016	EMA headquarters (London, UK)	Over 100 of the most senior patient and doctor representatives and EMA regulators
Dec 2016	EMA headquarters (London, UK)	Over 100 of the most elite actors representing all audiences of transparency and EMA regulators

During the meetings, over 40 of the most elite policy actors gave presentations on EMA's transparency policies or transparency in the European pharmaceutical domain more generally. The presentations lasted between 15 minutes and 1 hour. All presenters were senior actors representing either the EMA, the European Commission, industry, patient and doctor advocacy groups, or the medical community more broadly (e.g. data miners, opinion leaders, journal editors) (Table 4.3). They included executive directors, heads of departments, committee chairs, board members, vice presidents, founders of companies and medical journals, as well as actors with many other senior positions. All Type 1 events also included extended debate and discussion on EMA's transparency policies from attendees, whilst providing the investigator with opportunities to meet many audiences of EMA's policies in person (including presenters).

[21] Danish Medicines Agency

Table 4.3: Examples of positions held by elite speakers at Type 1 meetings

	Positions of the most elite speakers
EMA	Chair of the Healthcare Professionals' Working Party Chair of the Patient and Consumers' Working Party Chief Legal Counsel Deputy Executive Director Executive Director Head of Communications Head of Public Information and Stakeholder Networking Head of Safety and Efficacy Principal Scientific Administrator Senior Medical Officer
European Commission	Assistant Data Protection supervisor at DG-SANTE[22] Legal officer at DG-SANTE Senior representatives from the European Ombudsman's office
Industry	Chair at EFPIA Chair of the Innovation Board at the Association of the British Pharmaceutical Industry (ABPI) Director of ABPI. Pharmaceutical company SVP of External Scientific Relations and Patents at Lundbeck A/S
Patient and doctor groups	Board member of the European AIDS Treatment Group Chair of the European Association for Clinical Pharmacology and Therapeutics (EACPT) Director of Treatment and Access at the European Organisation for Rare Diseases
Others from the medical community	Co-founder of the Cochrane Collaboration Director of the Wellcome Trust; Executive Director of the Australasian Open Access Strategy Group Founder of AllTrials.net Founding editor of *PLoS Medicine* Head of Pharmacoepidemiology and Pharmacovigilance at AEMPS Representative of the International Society of Drug Bulletins (ISDB)

Second, four meetings can be categorised as workshops co-organised by the investigator and two colleagues (hereafter, 'Type 2' meetings) (Table 4.4). The meetings were held annually in June for every case study year, took place in four EU countries (Sweden, Spain, Denmark and Ireland), and lasted two days each. The meetings had between 17 and 20 elite delegates. The investigator took extensive notes and wrote anonymised summaries of 4-5 A4 pages after all four meetings.

[22] Director General for Health and Food Safety

Table 4.4: Dates, locations, and no. of attendees at each Type 2 meeting

Date	Location	No. of Attendees
June 2013	Uppsala (Sweden)	20
June 2014	Madrid (Spain)	19
June 2015	Copenhagen (Denmark)	19
June 2016	Cork (Ireland)	17

Attendees had a variety of the most senior positions in the pharmaceutical policy domain and represented EMA, NCAs, patient advocacy groups, industry, and academia (Table 4.5). At every meeting all delegates (including the investigator) either gave formal presentations (15-30 minutes) or extended commentaries (10-15 minutes) on EMA's transparency policies, which were followed by extended debate and discussion. All four meetings were held under Chatham House Rule[23] and therefore encouraged open and honest discussion on the effectiveness of EMA's transparency policies from multiple (and potentially conflicting) audiences. This meant that delegates' identities were necessarily anonymised (Table 4.5).

Table 4.5: Anonymised information on all attendees at Type 2 meetings (excluding academia).

	Attendees (anonymised)
EMA	4 management board level representatives
Industry	2 board level EFPIA representatives 6 senior pharmaceutical company representatives.
National regulatory authorities	18 senior representatives from either Britain, Denmark, the Netherlands, France, Germany, Ireland, Norway, Spain, Sweden or Switzerland. Positions of representatives ranged from Director Generals and Heads of Department to Chief Medical Officers and national representatives of EMA's scientific committees (e.g. the Pharmacoviglance Risk Assessment Committee).
Patient groups	2 senior supranational patient advocacy group representatives

Third, three meetings can be categorised as private meetings or EMA policy consultation events that for which the investigator was invited to by EMA regulators (hereafter, 'Type 3' meetings). All three meetings were held at EMA's headquarters and included discussions between EMA regulators, the investigator, and other academics. The first meeting was held in December 2013 and was attended by three EMA regulators, two NCA regulators, the investigator, and one colleague from academia. The second meeting was held in May 2014 and

[23] *see* https://www.chathamhouse.org/about/chatham-house-rule

was attended by 34 influential medical community academics (e.g. data miners from the Cochrane Collaboration) and at least ten senior EMA regulators (e.g. EMA's Chief Policy Advisor and Senior Medical Officer). The third meeting was held in September 2016 with nine EMA regulators, the investigator, and one colleague from academia. The meetings provided the opportunity to discuss EMA's transparency policies in-depth. At all three meetings the investigator recorded meetings with detailed notes.

Fourth, four meetings can be categorised as events with regulatory authorities operating outside the EU (hereafter, 'Type 4' meetings). Two meetings were held at the US FDA's Centre for Drug Evaluation and Research (Maryland, USA). They took place in December 2013 and April 2015 and were each attended by over 40 FDA regulators. A third meeting was held at Health Canada's headquarters (Ottawa, Canada). The meeting took place in April 2015 and was attended by over 150 Health Canada regulators. A fourth meeting was hosted by Swissmedic, the Swiss pharmaceutical regulatory authority, in Montreux, Switzerland, in September 2015. The meeting was attended by over 100 delegates including patient and doctor advocacy groups, industry representatives, EMA regulators, academia, and most board-level Swissmedic regulators. Meetings at regulatory authorities operating in other jurisdictions – such as the Japanese Pharmaceutical and Medical Devices Agency or the Australian Therapeutic Good Administration – could not be organised or attended due to resource constraints. All four meetings included presentations by the investigator and extended debate and discussion on EMA's transparency policies with attendees. The four meetings collectively provided Canadian, American, and Swiss perspectives on EMA's input transparency policies, which was essential for understanding the effectiveness of EMA's three main input policies as they all involve publishing data online and hence have global consequences (and global audiences).

The 18 elite meetings enabled the investigator to conduct two main methods for collecting evidence on the effectiveness of EMA's policies over 23 days. The first method adopted was direct observation. While formal direct observation might involve using specific instruments (e.g. tallying the occurrence of certain types of behaviour), this study adopted a more informal and detached approach or what some categorise as "nonstructured observations" (McKechnie 2008: 575). Such observations were considered as highly appropriate for this study as they are well suited for collecting data on an under-explored phenomenon and are well suited for studying phenomena over time (McKechnie, 2008). The investigator observed presentations

given by elite policy actors and debates between attendees throughout the meetings in what Gilham (2010) describes as the 'fly on the wall' approach. The investigator observed, for example, what presenters and attendees said, the words they used including their accounts, and their experiences of EMA's transparency policies.

Each type of meeting provided different opportunities for understanding the effectiveness of EMA's policies for multiple transparency audiences. For example, while more reserved statements on EMA's policies were observed at larger public events, the smaller scale Chatham House Rule and private meetings produced more candid and honest discussions. At all meetings the investigator paid careful attention to the reactions of all attendees and observations were made on presentations, questions and comments, and discussions made during breaks. Relevant case study evidence was recorded by hand, which produced a total of three field notebooks with 192 A5 pages each. At the end of each meeting the investigator also created summaries of the most important comments.

The second data collection technique adopted at all 18 meetings was to conduct unstructured informal interviews (*see* Robson and McCartan, 2016: 293) or what some methodologists categorise as "conversational interviewing" (Roulston, 2008: 128-129). This approach can be used "to generate verbal data through talking about specified topics with research participants in an informal and conversational way" (Roulston, 2008: 128). It enabled the investigator to discuss the regulators' transparency policies with meeting attendees in a friendly and informal atmosphere and to receive authentic reflections. This would have been much more difficult at policy meetings by, for example, conducting formal semi-structured or structured interviews (Roulston, 2008).

All informal interviews were conducted after elite speakers had presented on EMA's transparency policies. This enabled the investigator to frame discussions casually around the case study topic and research question. Interviews ranged from short chats to long in-depth discussions and took place during coffee breaks, lunches, dinners, meeting receptions, and dedicated 'networking' sessions. The investigator was able to collect evidence by discussing the effectiveness of EMA's policies with a multiplicity of attendees and elite presenters. The investigator was able to clarify the meaning and significance of presenters' comments, corroborate evidence with other actors, and collect and compare the perspectives of meeting

attendees (and hence different audiences of transparency). It was not feasible or appropriate to tape record such unstructured and informal interviews. Doing so would have significantly affected their spontaneity and informality (Robson and McCartan, 2016). Rather, key comments and points of clarification were written down when it became possible and summaries of key evidence were made after all 18 meetings and while the investigator's memory was still strong.

(4.7) Surveys

Two online surveys were conducted in order to collect data on the perspectives of patients and (medical) doctors[24]. Both surveys were launched simultaneously on 10th November 2014. The patient survey was completed on 23rd February 2015. The doctor survey was completed three months earlier on 28th November 2014. They were both hosted on an invitation-only online web-portal by Ipsos, an international polling agency headquartered in the UK. The raw survey data was analysed independently by the investigator.

(4.7.1) Patient and doctor samples

The patient sample had 1010 adult respondents that were each diagnosed with one of five long-term medical conditions. These were HIV/AIDS (N=177); idiopathic pulmonary fibrosis[25] (IPF) (N=146); multiple sclerosis (N=127); rheumatoid arthritis (N=252); and osteoporosis (N=218). All patient respondents were from one of four EU countries: France (N=224); Germany, (N=227); Spain (242); and the UK (N=317). Further demographic information was collected on respondents' sex, age, membership of patient organisations, length of time diagnosed with their medical condition, working status, household income, education, and race (Table 4.6), as well as their geographic region (Appendix A). All respondents had to answer two screener questions before agreeing to participate. This was to exclude respondents under 18 years old and those that had not been diagnosed with one of the five medical conditions. Ipsos's standard operating procedures also ensured that these two eligibility criteria were met.

[24] Summary results are also reported in two special issue articles in the *Journal of Risk Research* (Way *et al*. 2016; Löfstedt, *et al*. 2016).

[25] Idiopathic pulmonary fibrosis (IPF) is the most common, yet still rare, interstitial lung disease and there is currently no known cure. According to the British Lung Foundation (2015), almost 50% of individuals with IPF do not live longer than 3 years after diagnosis.

Table 4.6: Demographic data for the patient sample

	HIV/AIDS	Idiopathic Pulmonary Fibrosis	Multiple Sclerosis	Osteoporosis	Rheumatoid Arthritis
Male	81%	60%	38%	22%	49%
Age (average in years)	42.7	45.4	43.1	56.6	55
% in patient group	49%	66%	42%	20%	28%
Average years with medical condition	3.7	2.7	3.8	3.2	3.3
% working full time	45%	40%	37%	26%	43%
Household income (% less than £30,000)	64%	51%	53%	60%	54%
Education (% with Bachelor's degree)	44%	52%	39%	35%	36%
Race (% white)	83%	86%	91%	94%	94%

The doctor sample contained a total of 1005 medical doctor respondents that have all been in clinical practice for >3 and <35 years and currently work for 20+ hours per week. All respondents were from one of four EU countries: France (N = 254); Germany (N = 250); Spain (N = 251); and the UK (N = 250). In each sample country, approximately 50% were general practitioners (N = 483) and approximately 50% were specialists (N= 522) in treating HIV/AIDS (N = 124); IPF (N = 128); multiple sclerosis (N = 126); or rheumatoid arthritis/ osteoporosis (N = 144). In other words, doctor sample respondents were from the same four EU countries as patient sample respondents and were either general practitioners or specialists in treating the five patient sample medical conditions. Further demographic information was collected on doctor respondents' sex, years in clinical practice post-residency, weekly hours in clinical practice, type and size of practice, monthly number of patients treated, and whether they treated children/adolescents or adults over 18 years old (Table 4.7), as well as their geographic region (Appendix A).

Table 4.7: Demographic data for the doctor sample

		France	Germany	Spain	UK	All
Average number of years in clinical practice post-residency (years)		19	16	17	17	17
Average hours per week in clinical practice (hours)		49	48	40	44	45
Type of practice (%)	*Group*	22	46	26	48	35
	Solo	30	30	7	1	17
	Clinic	1	14	6	2	6

	Hospital	48	10	59	48	41
	Other	0	1	1	1	1
Approximate number of patients treated in last month (%)	*100 or fewer*	7	2	5	11	6
	101-200	21	12	18	25	19
	201-300	17	16	24	19	19
	301-400	18	24	15	14	18
	401-500	19	23	11	14	17
	501-600	10	10	10	9	10
	601-700	4	5	4	3	4
	701+	5	8	12	5	8
Size of hospital or surgical centre (No. of beds) (%)	*Fewer than 100 beds*	4	4	4	4	4
	100-299 beds	11	13	20	5	12
	300-499 beds	17	9	19	16	16
	500 or more beds	32	14	34	36	29
	Not applicable	35	60	23	38	39
Average % of patients that are…	*Children/adolescents*	15	10	9	14	12
	Adults aged 18 and over	85	90	91	86	88
Sex (%)	*Male*	68	72	70	78	72
	Female	32	28	30	22	28

The five medical conditions were chosen because they are all life-long chronic disabling diseases with no known cure. Although every human being could be categorised as a 'patient', individuals suffering from long-term disabling diseases differ in that they frequently have to make complicated decisions on medicines that have clear benefits but where the risks are not negligible (Mayer, 2011; also see Edwards and Elwyn, 2009). The samples also contained a variety of long term medical conditions including a rare disease (i.e. IPF). This was important because patients (1) have to make different (and difficult) benefit-risk decisions on medicines authorised to treat their conditions (e.g. different treatment options); (2) experience different levels of impairment and disability (e.g. those diagnosed with HIV/AIDS compared to multiple sclerosis); and (3) have different information sources available to them (e.g. patients with rare conditions have small patient group communities) (*see* Garcia-Retamero and Galesic, 2013 for further discussion; Baggot and Forster, 2009, Mayer, 2011).

The four sample countries were primarily chosen because they are all in the EU and so within EMA's jurisdiction. They were also all included in a general public survey conducted in 2012 by the investigator (and colleagues) (*see* Bouder, Way, Löfstedt *et al.* 2015). Therefore comparisons between the general public in 2012 and the results of this study could be made directly. Four rather than the full six countries surveyed in 2012 were chosen due to resource

constraints of recruiting individuals with medical conditions compared to members of the general public.

(4.7.2) Recruitment and representativeness

Two approaches were adopted for recruiting patients and doctors. The first targeted patients exclusively. The author and a colleague contacted over 25 patient groups including several EU umbrella organisations such as the European Patients Forum, the European AIDS Treatment Group, and the International Osteoporosis Foundation, as well as many other national-level organisations specialising in different target conditions[26]. Elite representatives from these groups were met at elite policy meetings (*see* section 4.5), through colleagues, or, in a few cases, through unsolicited e-mails.

Patient groups were all generous in providing advice on further revising the questionnaire and, in addition, sent email invitations to members through patient group email lists. A small donation of €10 was offered to each patient organisation for every completed questionnaire. However, although essential for adjusting the questionnaire itself, this approach resulted in a low response with only 79 respondents completing the questionnaire (8% of the final sample). One reason for such a low response was that patient group members are surveyed frequently (e.g. by other researchers or patient organisations). For instance, one patient group that agreed to participate had only recently finished surveying members in its biannual survey.

The second recruitment approach targeted both patients and doctors and was carried out in collaboration with Ipsos[27]. The remaining patients and all doctors were obtained through this second approach using online panels and quota sampling. Specifically, 931 patient respondents (92% of the final sample) and 1,005 medical doctors (100% of the final sample) were recruited. Ipsos have notably strict procedures and industry standard checks to preserve recruitment quality such as mechanisms to discourage professional responders and continually refresh respondents between surveys (Twyman, 2008; Ipsos, 2015). The agency also fully complies with the British Polling Council's requirements (British Polling Council, 2017).

[26] The investigator would like to particularly thank the following national-level organisations: Liga Reumatológica Española (LIRE); Esclerosis Multiple Espana (EME); Asociación De Familiares Y Enfermos De Fibrosis Pulmonar Idiopática (AFEFPI); Association Fibrose Pulmonaire Idiopathique (AFSEP); Pulmonary Fibrosis Trust; British Lung Foundation; and the Multiple Sclerosis Society.
[27] See Ipsos (2015) for a thorough explanation of the organisation's recruitment procedures.

Patient and doctors were recruited in slightly different ways. Patient respondents were recruited onto large and varied panels using email lists, banners, websites, text ads, search engine methods, and other techniques. They were offered incentive points – a common form of incentive for participants in online panel surveys – which helped reduce potential for response bias (Dillman, 2014). In contrast, doctor panellists were recruited by using an in-house call centre where potential respondents were contacted at their place of work. They could also sign up to the panel via the agency's website and refer colleagues by contacting the agency directly. Doctor respondents received an additional incentive of between £36 and £60 depending on their speciality area and country.

Once the panels had been created, patients and doctors meeting the study's requirements were sent e-mail invitations. Both response and completion rates were calculated (*see* Dillman, 2007 for a discussion).

Table 4.8: Number of quits, completes, invitations sent for each sample country, as well as the response and competition rates

		UK	**France**	**Spain**	**Germany**
Patients	*Invitations to participate*	5200	5000	4900	6000
	Quits once started	36	42	23	9
	Completions	274	215	228	214
	Response rate	5%	4%	5%	4%
	Completion rate	**88.39%**	**83.66%**	**90.98%**	**95.96%**
Doctors	*Invitations to participate*	4246	4215	4334	6489
	Quits once started	122	41	41	42
	Completions	250	254	251	250
	Response rate	6%	4%	6%	6%
	Completion rate	**67.2%**	**86.1%**	**85.96%**	**85.62%**

The response rates reported are extremely conservative estimates primarily due to the nature of Ipsos's recruitment procedures. The agency sent out a large number of invitations, but then established quotas for the number of respondents it accepted in each survey sub-sample (e.g. each medical condition for which patients were recruited). This meant that up to 100% of invitees could have tried to respond, but once the quota was met, all future respondents were ineligible to participate. Both surveys contained screener questions in order to ensure that respondents met eligibility criteria, which eliminated a substantial portion of the original

invitees from the response rate figures. The quit rate reported also only includes those individuals who quit the survey after being admitted to the survey, thus not accounting for individuals who were invited but who were ineligible.

Moreover, the 'representativeness' of the sample was considered far more important than the response rate itself (*see* Krosnick, 1999 for a discussion; AAPOR 2015; Cook, Heath, and Thompson 2000; Krosnick and Presser 2010). Survey methodologists emphasise that high response rates are often, optimistically, taken to denote low response bias, but this extrapolation does not necessarily follow, and response rate is only a proxy, at best, for (lack of) response bias (Krosnick, 1999; Krosnick and Presser 2010). The extent to which response bias exists amongst non-respondents is the most important issue rather than the percentage of invited participants who respond. This meant that another important advantage of using Ipsos was that they were able to ensure that the surveys had a robust sampling procedure. The polling agency drew respondents from large and varied sets of panel participants and has industry standard checks to preserve panel quality. Ipsos also offers competitive and appropriate incentives (such as incentive points), which helped to reduce potential for response bias (Dillman *et al*. 2014). Indeed, Ipsos is well-known as one of the most respected online surveying firms in the academic community and operates across 47 nations (Twyman, 2008; British Polling Council, 2017). Therefore in terms of systematic sampling the two surveys have much to recommend them.

(4.7.3) Questionnaire design

The patient and doctor questionnaires were created simultaneously over a two-month period in mid-2014 and were guided by the latest theoretical and empirical research on survey designs (*see* Marsden and Wright 2010). The questionnaires were first modelled on past questionnaires – originally designed by the investigator and colleagues – that were used to compare the views of US doctors (N=433) and US adults in 2011 (N=1,000) (Löfstedt *et al*. 2011), as well as European adults in 2012 (N=5,648) (Bouder *et al*. 2015). This enabled the investigator to make direct comparisons between this study's results and previous surveys. The questionnaires were also informed by two experimental studies conducted by the author and colleagues on a sample of general public respondents living in London (the UK) and Limburg (the Netherlands) (N=200) (Löfstedt and Way, 2016a), and Munich (Germany), and Madrid, (Spain) (N=200)

(Löfstedt and Way, 2016b). Several medically qualified NCA regulators also provided informal advice as well as 4 Ipsos employees who, for example, explained what design features the agency's systems could support (e.g. progress bars and response option ordering randomisation).

The first stage was to design the initial questionnaire. Necessary adjustments were made to the previous questionnaires first so that they were relevant and appropriate for patients and doctors. For example, respondents in the present study were asked to indicate the extent to which they 'agree' or 'disagree' (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree, don't know) with the following statement:

> I have good knowledge of how the European Medicines Agency (EMA) assesses the safety of **[relevant medical condition]** medicines. [Bold added for emphasis]

This question was also posed to respondents in the general public survey (Bouder *et al*. 2015). However, each relevant medical condition in the present study (e.g. multiple sclerosis or rheumatoid arthritis) was inserted in order to make the question relevant to different patient respondents or doctors. New and original questions were also developed that built on previous findings (e.g. follow-up questions), addressed new policy developments (e.g. EMA's clinical trial data policies), and investigated important issues that could not be posed to members of the general public (e.g. questions about specific medical conditions).

Both questionnaires were thoroughly pre-tested. Doing so was an essential part of the design process and helped to identify and correct weaknesses and errors (van Teijlingen and Hundley, 2002). Many of the questions had previously been rigorously tested in the US (Löfstedt *et al*. 2013) and Europe (2013) (Bouder *et al*. 2015)[28]. Although this strengthened the design, additional piloting was required after making numerous changes to the questionnaire. The patient questionnaire was pre-tested on a pilot sample of eight members of the European AIDS Treatment group (EATG) and received informal input from patient group representatives from EATG, the European Brain Council, and the British Lung Foundation. Concurrently, the doctor questionnaire was pre-tested on 6 medical doctors working for a pharmaceutical company

[28] To be clear, this included extensively piloting and conducting three studies on 433 American physicians, 1,000 American adults, and 5,648 European citizens (Löfstedt *et al*. 2013; Bouder *et al*. 2015).

(Biogen Idec.), several patient group representatives (e.g. working at EATG), and two randomly selected and anonymous UK doctors (via anonymous online interviews). After minor adjustments had been made, the English questionnaires were professionally translated by Ipsos into French, German, and Spanish. Each translated questionnaire was subsequently double checked by native speaking colleagues from relevant NCAs that were met at elite policy meetings (section 4.5). This resulted in each questionnaire receiving minor accuracy edits based on their recommendations.

The final patient questionnaire contained 23 closed and seven open-ended questions and lasted for an average of 14.17 minutes (Appendix B). The final doctor questionnaire contained 27 closed- and nine open-ended questions and lasted for an average of 19.14 minutes (Appendix C). They were each structured into 4/5 broad sections (Appendix A):

1. Screener questions
2. General communication of medicines information
3. Pharmaceutical regulatory authorities
4. [doctors only] Questions on specific documents; and
5. Background questions.

Screener questions. All respondents were asked screener questions to ensure they were eligible to participate. Patient respondents were excluded from the study if they were under 18 years old (i.e. those born in 1996 or more recently), were not diagnosed with one of the five targeted medical conditions (i.e. HIV/AIDS, IPF, MS, osteoporosis or rheumatoid arthritis) or had been diagnosed for less than one year. Ipsos's standard operating procedures also ensured that respondents were, indeed, over 18 years old and were diagnosed with one of the medical conditions reported. Doctor respondents were excluded if they had been in practice post-residency for less than 3 and more than 35 years, were not a general practitioner or specialist in treating at least one of the five targeted medical conditions (i.e. HIV/AIDS, IPF, MS, osteoporosis, or rheumatoid arthritis), and currently worked in clinical practice for less than 20 hours a week. Screener questions were followed by a consent form that included essential and important practical and ethics-related information about the study such as informing respondents their answers were anonymous and that they can withdraw at any point.

General communication of medicines information. All respondents were asked various questions on the general communication of medicines information. This includes questions on the availability and quality of information, trust in different sources of advice, effectiveness of government, and their confidence in taking medicines. For example, respondents were asked: "Would you say that the amount of information about medicines currently available is too much, the appropriate amount, or too little?" (Too much, Appropriate amount, Too little). Questions ranged from very general questions about the quantity and quality of information available to more specific questions on the ease of obtaining information and trustworthiness of specific sources of medicines advice (e.g. from doctors, patient advocacy groups, medical journals).

Pharmaceutical regulatory authorities. All respondents were asked about the EMA and their relevant NCAs. National authorities varied between sample countries and are all recognised by EMA as the main organisation responsible for pharmaceutical regulation in each sample country (i.e. the National Competent Authority [NCA]) (Table 4.9). Respondents were first asked whether they had heard of their relevant NCA and, if so, whether they had positive or negative impressions of them. All respondents then read a short paragraph explaining who their NCA was and its responsibilities. For example, UK respondents were asked to read:

> *"The MHRA (Medicines and Healthcare Products Regulatory Agency) is the medicines regulator for the United Kingdom. They are responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe. We are now going to ask you a few questions on your perceptions of how medicines are regulated in the UK."*

This sought to ensure that respondents who had mistakenly identified their NCA in the previous question were corrected and that those who said they had not heard of them were now aware of them (that is, in order to understand subsequent questions). Respondents were then asked a series of questions examining their awareness and knowledge of their relevant NCA. This was followed by several questions that their trust in pharmaceutical regulatory authorities, which were adapted from a comprehensive review of the trust literature (Earle, 2010) and a follow-up commentary on trust-related research designs (Siegrist, 2010). These questions and the descriptive paragraph were then repeated for the EMA. Each NCA and EMA paragraph was written by the investigator and then checked by regulators at a relevant NCA in all sample countries.

Table 4.9: Relevant NCAs chosen for each sample country including their acronyms and full English language name

Sample Country	Acronym	Full English Language Name
France	ANSM	National Agency for the Safety of Medicine and Health Products
Spain	AEMPS	Spanish Agency for Medicines and Health Products
Germany	BfArM	Federal Institute for Drugs and Medical Devices
United Kingdom	MHRA	UK Medicines and Healthcare products Regulatory Agency

Questions on specific documents. Medical doctor respondents were asked several questions about various regulatory documents that EMA have or are proposing to make publicly available. This includes clinical study reports and periodic safety update reports (PSURs). Respondents were asked to indicate their knowledge and familiarity with regulatory documents, opinions on making more safety-related information publicly available, and confidence in explaining safety information contained in regulatory reports to patients.

Background questions (Tables 4.6-4.7). All respondents were asked general background/ demographic questions on their age and sex. Patient respondents were also asked about their employment status, geographic region where they live, household income, educational qualifications, and ethnicity, as well as how long they have been a member of a patient advocacy group (if at all). Doctor respondents were also asked about the geographic region where they work, the size of the hospital or surgical centre where they work, approximately how many patients they treat a month and the percentage of adults versus adolescents/ children they treat.

These survey questions are explained further in Chapter VII (i.e. before presenting the results) as the specific choice of questions are directly linked to emerging case study findings.

(4.8) Analysing the evidence

The evidence collected from the four research methods – documentation, observations, interviews, and surveys – was analysed over four empirical chapters (Chapters V-VIII).

Chapter V. The first empirical chapter provides a detailed exploration and overview of the EMA's transparency policies in historical perspective spanning from its establishment in

January 1995 to December 2016. While much of the analysis draws on documentation (including archival analysis), observations and interviews were also used from 2012 - 2016. The chapter first provides a background on the establishment of EMA in 1995 as an independent and transparent decentralised EU regulatory authority. It then goes on to explain the evolution of the agency's policies including key milestones. A draft version of the chapter was also reviewed by two senior EMA regulators to check for accuracy. Extracts from the chapter were then peer-reviewed at the *European Journal of Risk Regulation* and subsequently revised as part of a historical comparison of transparency at EMA and EFSA (Way and Löfstedt, forthcoming).

Chapter VI. The second empirical chapter focuses on the three sub-units of analysis. A detailed explanation of clinical trial data is first provided. Using extensive documentation, observations and interviews, each policy is then examined in turn. The goals and audiences of each policy are given systematic attention and the main purpose of the chapter is to present the case study results.

Chapter VII. The third empirical chapter presents the results of the patient and doctor surveys. Descriptive statistics were used as well as statistical significance tests where appropriate. For each individual question reported in the results, the question specific design (e.g. ratings scales, ordering of response options) as well as statistical tests are explained. IBM SPSS Statistics Version 22 and Microsoft Excel were used in analysing the results and creating graphs. For the open-ended data, the UK sample was first coded, analysed, and categorised by the investigator. The same process was then conducted independently by a colleague. All codes were discussed and new categories created when there was disagreement. Once the UK results had been coded and analysed researchers from relevant sample countries were recruited (i.e. native French, German and Spanish speakers) to code and categorise relevant open-ended data.

Chapter VIII. The fourth empirical chapter addresses the research question directly and evaluates how effective EMA's transparency policies have been in achieving its public policy objectives. In particular, it brings together the three previous chapters in order to critically examine the effectiveness of EMA's transparency policies using data from perspectives of six main audiences holistically (Table 4.1). Further supportive evidence is also used from the four case study research methods where appropriate. After examining the three sub-units of

analysis, the evaluation returns to the main EMA case study unit of analysis. This is important because, as Baxer and Jack (2008) explain, a major pitfall "occurs when the case study focuses on the subunit level and fails the return to the larger unit of analysis". Therefore the final empirical chapter returns to the larger unit of analysis on the effectiveness of EMA's input transparency policies.

(4.9) Limitations

One main limitation of this study was that a single case rather than a multi-case design was necessarily chosen (section 4.4). By focusing on EMA's transparency policies and the European pharmaceutical domain, other risk regulation authorities and policy domains were excluded from the analysis. Inasmuch as multiple experiments can verify findings from a single experiment, multiple case studies can verify findings from singe case studies (Yin, 2009). However, a multiple case study could not be conducted primarily due to resource constraints. A single case design also provided other advantages including enabling multiple sub-units of analysis to be examined in great depth, which would not have been possible with multiple cases. This was particularly important because there has historically been little empirical research on transparency in risk regulation and so this study needed to be both exploratory (i.e. to test the original typology) and explanatory (i.e. to test EMA's policies) (Chapter II) (Etzioni, 2010; Cucciniello *et al*. 2017). This means that additional case studies on other regulatory bodies should be conducted in the future – such as on other decentralised EU agencies – in order to compare the results from the EMA case (including analytic generalisations) (*see* Chapter XI for a discussion).

Another main limitation of this study was that some audiences of EMA's transparency were not included at all. For example, journalists (and other intermediaries) interpreting data and communicating data. Rather, this study targeted the main audiences of EMA's transparency policies that are the main targets of the regulators' transparency policies (Table 4.1). This means that the full net effects of EMA's transparency policies for all audiences could was not addressed.

A third main limitation of this study was the main audiences of EMA's transparency policies (Table 4.1) were also not examined directly (except for patients and doctors). In other words, the study did not collect evidence from the perspectives of the actual individuals that are

expected to directly or indirectly use data made publicly available by EMA. For example, the study does not include surveys of the clinical trialists or systematic reviewers that are expected to re-use EMA's scientific data. Rather, it collects information from the perspective of the most elite actors and it follows the policy process. This was a strategy that was necessarily adopted (section 4.4).

The main method for collecting evidence from patients and doctors, the two audiences that evidence was collected, also had its own limitations. First, the survey results do not seek to bring together the full range of perspectives on EMA's transparency policies. This would require examining the perspectives of all different actors including external researchers wishing to reuse medicines data (e.g. clinical trial reports) (Doshi and Jefferson 2013a). Rather, this study contributes empirical evidence from the perspective of an understudied groups of actors that has received a distinct lack of attention in the debate about EMA's policies (i.e. patients).

Second, the study did not examine the positive benefits for patients from other actors reusing medicines information. A main goal of the regulators' transparency policies is to enable 'outsiders' to reuse its data enabling high-quality analyses to improve the pharmaceutical evaluation system (EMA 2014a, 2014b, 2016a). Examining the full net effects of EMA's transparency policies from the perspective of patients would therefore require including empirical evidence on the positive, negative and/ or limited effects of enabling outsiders to reuse medicines information that is expected to, in turn, benefit patients (e.g. by receiving safety and more intensively and extensively investigated medicines). What will be needed is further qualitative and quantitative empirical research examining the full net effects of EMA's transparency policies from the perspective of all actors.

Third, the study does not directly examine whether EMA's transparency policies have or have not resulted in fully informing patients about its scientific and non-scientific activities. It did not, for example, examine whether patients have a better or worse understanding of the agency's activities (e.g. through testing their knowledge before and after the policies were introduced) or whether patients would be able to understand the information contained in the documents released by the agency (e.g. comprehension tests). Rather, the study examined some of the complexities of communicating about scientific and non-scientific regulatory activities and, in turn, identified how these are likely to impact on the success of EMA's transparency

policies and its goals. Furthermore, surveys were generalised and not on specific policies (see Way *et al*. 2016). Rather than examining EMA's specific policies and their effectiveness, the surveys examined the perspectives of EMA's policies based on the regulators' logic. It does not measure and evaluate the actual data and information that is released but rather seeks to understand the perspectives of patients and doctors

Chapter V: TRANSPARENCY AT EMA IN HISTORICAL PERSPECTIVE

This chapter provides a historical analysis examining how EMA's transparency polices have evolved over time spanning from its inception in 1995 to December 31st 2016[29]. The decentralised EU agency provides an excellent case of a European regulator that has been criticized for "not being transparent enough" despite consistently demonstrating a firm commitment to the concept (e.g. by meeting and going beyond legal requirements) (EMA, 2009, 2016). EMA is responsible for pharmaceuticals and specifically "the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use" (EMA, 2017a). This chapter and thesis is, however, limited to the agency's evaluation of medicines for *human use* and will therefore exclude activities relating to veterinary medicines (Chapter V). It also pays particular attention to EMA's transparency policies regarding its scientific evaluation of medicines (e.g. in the Committee for Medicinal Products for Human Use [CHMP] and the Pharmacovigilance Risk Assessment Committee [PRAC]). Therefore other core regulatory activities such as inspections are beyond the scope of this chapter and thesis.

The chapter is structured as follows. First, a contextual background explaining what EMA is and why it was created is provided. This includes an understanding of why the agency committed so strongly to transparency from day one. Second, three distinct phases in the evolution of transparency at EMA are identified and discussed in turn. Each phase includes a description and explanation of the types of transparency policies introduced by the agency as well as how outsiders have viewed its approach along the way.

(5.1) Background and formation

In January 1995, EMA (originally the European Agency for the Evaluation of Medicinal Products [EMEA]) opened its doors (EMA, 1995). EMA was not created "from scratch" but was the culmination of 30 years of pharmaceutical legislation (Sauer, 1995; Demortain, 2011; Groenleer, 2009). Following the Thalidomide birth defect tragedy (Stephenson and Brynner, 2001; Botting, 2002; Permanand, 2004), the first EU pharmaceutical legislation was adopted

[29] The end of 2016 provides a good cut-off date as this PhD thesis was finalised in January 2017. The Chapter is also under review at the *European Journal of Risk Regulation* (Way and Löfstedt, 2016). Hence much of the text included in this paper is repeated here.

in 1965 (Directive 65/65/EEC). Member states were required to create and thereafter manage a formal evidence-based marketing procedure based on the principles of "quality, safety and efficacy" (Demortain, 2008). To be clear, prior to the 1960s only rudimentary forms of governmental and regulatory control existed in Europe (*see* Orzack *et al*., 1992; Vogel, 1998). A second milestone came in 1975 when the Committee for Proprietary Medicinal Products (CPMP) (later renamed the Committee for Medicinal Products for Human Use [CHMP]), a scientific committee comprised of representatives from all member state regulatory authorities, was established (Permanand, 2004; Groenleer, 2009). The new committee's role was advisory (Vogel, 1998), which (crucially) meant that member states "maintained the right to deny approval" of a medicine regardless of the committee's decision (Vogel, 1998: 3; Orzack *et al*., 1992). For instance, CPMP could provide advice to a member state "in case they were reluctant or unwilling" to recognise marketing approvals authorised in other nations and frequently did so (Groenleer, 2009: 144). Seventeen years later in 1987 it became mandatory for member states to consult the CPMP before authorising biotechnology products (e.g. recombinant DNA, hybridomes/monoclonal antibodies and cell cultures) but not for all medicines (COM, 1988: 16). An increasing number of measures and legislative requirements were therefore introduced between 1965 and 1995 in seeking to improve and incrementally 'Europeanise' pharmaceutical regulation.

The European Commission went further in its 1985 White Paper on *'Completing the Internal Market'* (COM, 1985). Amongst many other measures needed to complete the single European market (for goods, persons, services and capital) (Cecchini, 1988; Orzack, 1992), the Commission made clear that "obstacles to the free circulation of pharmaceutical products and high technology medicines" needed to be eliminated (Orzack, 1992: 856). However, concerns quickly surfaced that it would not meet the strict December 1992 internal market deadline for pharmaceutical products (Callingaert, 1988; Cecchini, 1988). In particular, a 1988 review (COM, 1988) detailed the experiences and shortcomings of CPMP and the European pharmaceutical authorisation system (*see* Orzack *et al*., 1992 or Vogel, 1998 for discussions).

One of the most important barriers to integration was that European pharmaceutical regulation was fragmented. Pharmaceutical companies were required to obtain marketing authorisations from individual member states that had lengthy and varying procedures, or as Currie (1989: 770), from Merck's regulatory affairs department, put it: there were barriers due to "differences

in procedures, standards, data requirements and the time required to reach a decision on the application" between member states. Writing in 1989, Kaufer (1989 In: Vogel, 1998: 2-3) explains further:

> *"The free movement of drugs in the European Community is not only hindered by the fact that the national competent authorities render different value judgements on the merits of therapeutic approaches and on issues of relative benefits and risk of drugs. On top of these drug specific differences come health-policy specific differences in the control of the social-security system, and industry specific differences in the control of drug industry's prices and profit, and differences in the extent to which national governments assist their national drug industry".*

These issues and others collectively showed that the traditional decentralised authorisation system had failed (Deomartain, 2006; Gehring and Kraphol, 2007; Groenleer, 2009).

Establishing a new centralised procedure – coordinated by a new decentralised EU agency – was subsequently viewed as a way of meeting the strict internal market deadline (Groenleer, 2009). Unlike EFSA, for example, transparency was therefore not a central reason for establishing EMA (Way and Löfstedt, forthcoming). With that said, there is strong evidence that the Commission was concerned about the independence and fairness of member state regulatory decision-making at the time and viewed transparency as an effective measure in tackling this issue. In particular, the Commission was concerned that member states were favouring domestic pharmaceutical companies (Sauer and Hankin, 1987; Cecchini, 1988; Vogel, 1998). For instance, according to the 1988 Cecchini report on the *'Benefits of a Single Market'*, contemporary research showed that member state pricing systems "may operate with discriminatory bias [...] [that] clearly operate in favour of the domestic manufacturer" (Cecchini, 1988: 68). Therefore enhancing transparency in the control of drug pricing was viewed by the Commission as an important measure for reducing member state bias (COM (86)765 of 12/23/1986). However, its implementation was considered to be heavily constrained by the traditional member state regulatory system (*see* Sauer and Hankin, 1987: 643).

Before the agency opened its doors in January 1995 there were clear signs of its future commitment to transparency and openness. In the agency's very design, transparency was viewed as essential for maintaining independence from the agency's many stakeholders including industry but also member states and the Commission. In particular, EMA's first Executive Director, Fernand Sauer, was acutely aware of the need for close collaboration with

these stakeholders in order to function effectively yet remain independent and accountable (Sauer, 1995, 1997; Demortain, 2008; Gehring and Kraphol, 2007). The agency would have to receive its funding from industry (through licensing fees), which is incidentally the same for most other pharmaceutical regulatory bodies (e.g. MHRA, FDA and Health Canada) (Breckenridge *et al*. 2005), but also the Commission. Unlike the US FDA but similarly to EFSA, EMA would not have its own 'in-house' expertise (Kingham *et al*., 1994). Rather, EMA was designed to be a coordinator and "hub of multi-levels actors" (Sauer, 1995; Groenleer, 2009). The highly technical nature of pharmaceutical scientific expertise, required for evaluating marketing applications that can amount to over 250,000 pages of highly technical data (Gehring and Kraphol, 2007), meant that most experts on EMA's scientific committees would necessarily have 'links' with industry (Sauer, 1995, 1997). Patients and doctors would also have to rely on expert judgement and evaluation of medicines as they will (usually) be unable to do so themselves (Feick, 2002) or as Gehring and Kraphol (2007: 211) put it: information is "typically asymmetrically distributed between producers and consumers" in pharmaceutical evaluation. Furthermore, the agency's scientific committees (e.g. CPMP/CHMP) were made up of representatives of the NCAs (i.e. member state regulatory bodies) and so even its core activity (medicines evaluation) involved possibility for bias. Transparency and openness were thus viewed as key to ensuring independence (Sauer, 1995).

These delicate independence challenges (and others) along with the need to have close collaboration with various stakeholders were viewed as important reasons for Sauer (1995) and others (e.g. the first Chairman of the Management Board, Strachan Heppell [1995]) to commit to transparency right from the start. Transparency was seen as an essential tool or principle for ensuring the agency could carry out its scientific activities independently. Doing so would allow anyone to scrutinise its opinions and decision-making and, in turn, promote accountability. In other words, 'outsiders' could 'see for themselves' that the agency and its committees were independent of industry, member states and the Commission, all three of which could potentially affect, or be perceived to be affecting, scientific rigour and independence.

(5.2) Establishing an independent agency (1995-2000)

After nominating Fernand Sauer, former Head of Unit for the Commission's Pharmaceutical and Veterinary Medicines Division, as EMA's first Executive Director in 1994, the newly established agency began operating in January 1995. As shown in all of EMA's first six annual reports (EMA, 1995, 1996, 1997b, 1998a, 1999, 2000a), the Executive Director and Chairman of the Management Board strongly advocated transparency and openness during the agency's formative years (Sauer, 1995; 2000; Heppell, 1999). For instance, in EMA's 1999 report, Strachan Heppell made clear that:

> "*The board has from its early days placed a great emphasis on accountability and transparency. Its policy has been that the Agency should explain what it is doing, why it is doing it and whether it has succeeded in meeting its performance targets. The Board has consistently believed that if this is done, the Agency will perform well and secure the confidence of the public"* (Heppell, 1999: 7).

The agency's first transparency policy was to introduce European Public Assessment Reports (EPARs) (Sauer, 1997), which was legally based in the agency's founding legislation (*see* Article 12 of Regulation (EEC) No. 2309/93) (Lekkerkerker, 2005: 35). The purpose of EPARs was to provide quality information to healthcare professionals and patients (Sauer, 1998b) and was promoted as "a useful means of ensuring transparency and subjecting EMA's activities to effective public auditing" (EMA, 1996: 23-34). Specifically, an EPAR was published for every medicine and "set out the scientific assessment carried out by the agency, together with the summary of product characteristics[30] and the patient leaflet[31]" (Sauer, 1998b: 1078). The first EPAR was published in the agency's very first year of operation for Gonal-F, a medicine developed by the then small pharmaceutical company, Serono (Sauer, 2009). Sauer (1995: 6) made clear that "better information for consumers is an absolute must for a more rational use of medicines, which will lead to improvements in public health and benefit health care budgets".

During its first six years of operation, EMA went on to introduce many other transparency initiatives. Three standout policies included publishing a list of scientific committee experts in

[30] "A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively" (EMA, 2015).
[31] "The leaflet in every pack of medicine that contains information on the medicine for end-users" (EMA, 2015).

1996 (EMA, 1996) and subsequently posting it online in 2000 (EMA, 2000a), the early publication of scientific committee opinions (EMA, 2000a) and publishing summaries of opinions on marketing applications whether they are negative or positive (EMA, 2000a). Another main activity was to continually develop EPARs such as through conducting a technical workshop in 1998 followed by improving the scientific and linguistic quality of the summary of product characteristics, package insert leaflets, and product labelling (EMA, 1999).

During the early years, other perhaps more mundane yet essential activities included setting-up a dedicated service for dealing with disseminating information (EMA, 1996) and creating and updating an Internet homepage (Sauer, 1995; EMA, 1998a, 2000a). Indeed, in the mid-1990s, creating a website was viewed as an important transparency measure (that could enable further transparency mechanisms) (Sauer, 1997: 97) and exemplifies how the Internet itself was a key contributing factor in the rise of so-called 'internet-mediated' transparency policies during the late 20th Century (Meijer, 2009). Furthermore, EMA created rules on access to documents (EMA, 1997a), a code of conduct for committee members (EMA, 1999), a code of good administrative behaviour (recommended by the ombudsman) (EMA, 1999) and launched a public document catalogue (EMA, 2000), amongst other procedural based transparency activities.

Beyond improving the amount and especially the quality of information available to 'outsiders' (including patients and healthcare professionals), a central pillar of EMA's transparency strategy was to communicate effectively with interested parties and stakeholders (Sauer, 1998a). In so doing, EMA interacted frequently with representatives from consumer groups (e.g. the European Consumers Organisation), industry (e.g. EFPIA), healthcare professionals and patient groups (e.g. EATG) such as during regular quarterly meetings (EMA, 1998), info-days (EMA, 1997b, 1998), ad hoc meetings (Sauer, 1998, 2009) and even, as Sauer (2005: 8) notes, "football matches". These efforts to ensure interaction with interested parties and stakeholders is perhaps not surprising considering there "were real worries" about whether EMA would succeed (Heppell, 2005: 9) because of the aforementioned challenges concerning independence and ensuring the agency maintained scientific rigour that was free from conflicts of interest. Indeed, many of EMA's early transparency initiatives were preceded by public consultation periods to help ensure its transparency goals were achieved.

The agency also conducted two workshops on transparency in 1997 and 2000 (EMA, 1997a, 2000b). When summarising the outcomes of EMA's first transparency workshop (EMA, 1997a), Strachan Heppell and Dietrich Henschler, a European Parliament representative on EMA's management board, prominently emphasised the relationship between transparency, information and communication:

> *"One of the primary concerns of the EMEA must now be the proper communication of information on medicines to patients [and] health care professionals […]. The EMEA, with the help of national authorities, will continue to work on how best to improve user information – including better involvement of consumer, patient and relevant groups"* (EMA, 1997a).

High quality dialogue and communication with all agency stakeholders (including patients and healthcare professionals) was thus viewed very highly by the regulators.

Despite introducing many transparency initiatives (including public workshops and consultations), the regulators, as Sauer (1998b: 8) put it, "inevitably" came under closer scrutiny. One of the most public criticisms came from the International Society of Drug Bulletins (ISDB), a society involved with disseminating medicines information to doctors (ISDB, 1998; Abbasi and Herxheimer, 1998). In particular, ISDB presented the results of an analysis of nine EPARs and expressed concerns over their quality (e.g. lack of clarity, variability of presentation styles, and inclusion of data solely from industry) (ISDB, 1998; Abbasi and Herxheimer, 1998). In response, EMA established continuing dialogue with ISDB including a detailed response to the society's initial EPAR analysis (EMA, 1998b). Another early criticism of EMA's transparency policies came from Abraham and Lewis (1999: 1666), two academics, who strongly argued in 1999:

> *"Despite the rhetoric of the European Commission and of the EMA supporting greater freedom of information, the European procedures of medicines regulation remain opaque to public scrutiny".*

The authors, in turn, demanded that EMA enhance transparency further to enable external public scrutiny and that, without doing so, 'outsiders' would have to assume regulatory capture by industry (Abraham and Lewis, 1999, 2000). According to Keleman (2002: 102), the agency also received criticism from a few MEPs (Members of European Parliament) who were concerned member states would become too dominant in the agency's activities, which could

lead to unscientific opinions based on national interests. However, in many cases it was actually industry that was the most vocal advocate of EMA enhancing transparency. For instance, one of EMA's early transparency initiatives, of publishing a summary of both positive and negative CPMP scientific opinions on the day of adoption by scientific committees, was initially proposed by EFPIA (a Brussels-based trade association representing industry) (EMA, 2000c: 1).

In addition, EMA had several teething problems with implementing and developing some of its early transparency policies. While EPARs were, according to Sauer (1998: 1078), "bound to be difficult to implement", the 1997 transparency workshop highlighted other difficulties. This includes issues of commercial confidentiality with releasing information on medicines developed by pharmaceutical companies and, as an FDA representative commented, transparency will have "significant resource implications" for EMA (EMA, 1997a). In 1998, the agency commented in its annual report that "as a matter of principle, details of applications submitted to EMA remain confidential" (EMA, 1998a: 16). In addition, despite freezes in agency recruitment (Sauer, 1998a: 8), CPMP reported that it had an increasingly demanding workload from publishing EPARs (e.g. in order to make sure they were accurate and readable for different needs) (e.g. EMA, 1999: 30).

Despite these early challenges, EMA's commitment to transparency and openness as well as including interested parties was viewed extremely positively by the majority of its many stakeholders (Groenleer, 2009). In particular, although there were some criticisms of EPARs (e.g. ISDB), they were viewed as an innovative and progressive transparency policy by many (Abbasi and Herxheimer, 1998; EMA, 2005a) or as Frits Lekkerkerker (2005), Chair of the Dutch Medicines Evaluation Board (MEB), commented in 2005: "The publication of the first EPAR was a major step forward in the transparency of regulatory agencies". Writing in the *British Medical Journal* in 1998, Kamran Abbasi, BMJ Assistant Editor, and Andrew Herxheimer, emeritus fellow UK Cochrane Centre, echoed these words when commenting that "in publishing public assessment reports, the European Medicines Evaluation Agency is far ahead of most national licensing authorities-which are still notoriously secretive" and that the agency has demonstrated that it is "open to criticism" (Abbasi and Herxheimer, 1998: 898).

In its '*Celebrating 10-years'* anniversary book (EMA, 2005a), contributions from a variety of stakeholders also made clear that the agency was successful in promoting transparency and inclusive decision-making in its early years including with patient groups (Le Cam, 2005: 80; Baker, 2005: 84). For instance, Rodney Elgie, President of the European Patient's Forum, commented:

> *"The contribution from patients is both visible and meaningful: all too often in other areas patient involvement has proved illusory or tokenistic. For this the EMA should be congratulated"* (Elgie, 2005: 78).

Or as Alastair Kent, President of the European Genetic Alliances Network, said:

> *"Those setting up the Agency […] were sensitive to patients' refusal to be patronized, and brave enough to see this as an opportunity for the new institution to commit itself to openness and transparency. […] Trust in the regulatory system and confidence that medicines are safe and effective can only benefit from this continued commitment"*. (Kent, 2005: 82).

Furthermore, in 2001 the Commission completed a large formal review and analysis of the agency (*see* Cameron McKenna and Anderson Consulting, 2001). The detailed report found, amongst many other findings, that both industry and member states supported the new centralised procedure and appreciated the work of EMA (ibid, 2001). Gehring and Kraphol (2007: 209) highlight one of the reports main findings:

> *"Over 90 per cent of the applying companies and all regulatory authorities of the then fifteen member states expressed their satisfaction with the [centralised] procedure, while the two principal consumer groups – physicians and patients – were only slightly less positive"*.

Therefore the early transparency years were evaluated very positively by the large majority of EMA's stakeholders and interested parties.

(5.3) Maintaining and strengthening transparency (2001-2009)

On 3rd January 2001, Thomas Lönngren, former Deputy Director-General of the Medical Products Agency in Sweden, replaced Sauer as Executive Director of EMA. Lönngren built on the transparency legacy of his predecessor and guided the agency through a period of

"consolidation" (Sauer, 2005, 2009; EMA, 2003a, 2007). During the initial four year period, EMA maintained and strengthened its commitment to transparency. The agency created new ways of engaging with stakeholders such as holding its first patient organisation workshop in 2002, which was viewed as "an additional initiative to improve transparency" and a "unique forum" that would complement other patient engagement activities (Lönngren [2002] In: EMA, 2002a: 1), creating working groups to discuss transparency issues (e.g. the organisation matters working group) as well as additional info-days and meetings with stakeholders (EMA, 2002b, 2003b).

However, the main trend was the development of an increasingly sophisticated and strategic approach to transparency. The agency was aware that it would have to prepare for new responsibilities from the Commission (EMA, 2001), accommodate the EU's enlargement in 2004 (including the introduction of ten new national regulatory authorities) and make substantial legally binding changes based on the EU's upcoming 2004 pharmaceutical legislation (EMA, 2002b, 2003a, 2004a). This meant that some of the main activities between 2001 and 2004 included introducing a "phased implementation" of the outcomes of its 2000 transparency workshop (EMA, 2001a), hiring a press officer (EMA, 2001a), creating a new risk communication unit (2001a), creating a working party dedicated to transparency, developing a risk management and communication strategy (2002b) and creating a good corporate governance strategy (EMA, 2003a). Indeed, these strategic activities would enable the agency to prepare for the major new developments ahead and its eventual expansion from a "very small agency with 150 staff" to one with more than 850 in December 2010 when Lönngren stepped down (Lönngren, 2010).

Furthermore, EMA had to deal with several other challenges such as coming into financial difficulties in 2002 resulting in curtailing non-essential core activities (due to receiving fewer than expected marketing applications) (Lönngren, 2002, 2003) as well as safety concerns associated with, for instance Baycol, Vioxx and COX-2 inhibitors (Lönngren, 2010; Löfstedt, 2007, 2010). Nevertheless, the agency pushed ahead with several new policies including holding a public consultation on transparency in 2003, which proposed eleven new initiatives relating to, for instance its website, EPARs, interaction with stakeholders, introducing a question and answer document for patients, and others (EMA, 2003a).

EMA's reflection book on its first ten years (EMA, 2005a) highlighted that up until 2005 (at least), the majority of stakeholders and interested parties continued to be impressed and happy with the agency's commitment to transparency and independence (also *see* Louet, 2004). With that said, between 2001 and 2004 (i.e. during Lönngren's first few years) there were some strong criticisms of the agency's work and approach to transparency. Most notably, Silvio Garattini, from the Mario Negri Institute for Pharmacological Research, was particularly critical of the agency's scientific work. Garattini (2005: 88), a former CPMP/CHMP member, argued that EMA had not moved quickly enough on transparency and lacked sufficient independence from industry:

> *"Transparency is still far from being achieved. Too many promises have been made in these years, with very little change actually implemented".*

Concerns were also expressed about the independence of the scientific committee including a distinct lack of scientific debate (e.g. suggestions of members favouring national interests), the undue influence and positon of the pharmaceutical industry on scientific decision-making, and the lack of transparency at the agency with arguments that EMA is secretive and that there is "no reason to hide data" essential for outsiders (e.g. to understand why a new drug has been approved) (Garattini and Bertele, 2007: 335; Garattini, 2005; Groenleer, 2009). Thus one main criticism was that the agency had moved too slowly on transparency and was not independent enough.

In 2004 the new pharmaceutical regulation was passed into law (Regulation (EC) 726/2004, Directive 2004/27/EC, Directive 2004/28/EC). Along with providing the agency with wider responsibilities and strengthening its post marketing surveillance, the EU legislation placed a new emphasis on transparency and patient information with several legally binding requirements. These included:

> *"…improve[ing] product related information [such as] publication of summary of the European public assessment report (EPAR) in a manner that is easily understandable to the public, the publication of withdrawals of marketing authorisation applications prior to an opinion, and the publication of marketing authorisations"* (EMA, 2005b).

In light of the new legislation, EMA's management board agreed on a new strategic '*Road Map to 2010'*, which included a continued emphasis on transparency and communication (Louet,

2004; EMA, 2005c). The road map committed EMA to a step-wise increase in its transparency efforts and set-out how it would achieve its goals (EMA, 2005b, 2009). One particularly notable action was for the agency to:

> *"Follow-up initiatives to improve the Agency's transparency and communication, with special emphasis on the provision of useful, clear and comprehensive information to patients/users of medicines and health care professionals"* (EMA, 2005b).

Indeed, the 2010 document clearly emphasised that effective communication of information was central to its transparency policies.

In the following four to five years, and in-line with its '*Road Map to 2010'*, the agency both met and went beyond its legal transparency requirements in both its scientific and non-scientific operations (EMA, 2009). Some of the most notable initiatives included publishing information on medicines that had been given 'orphan' (rare) drug status including the drug's name and condition it treats (EMA, 2004), creating an EU public medicines database (EMA, 2005c), launching EudraPharm (which contains information on EU medicines) (EMA, 2006), publishing summaries of EPARs, question and answer documents, and information on withdrawn applications (EMA, 2006), as well as publishing peer-review articles with agency opinions and perspectives (EMA, 2008). The agency also created new policies on handling conflicts of interest and began publishing declarations of interest online (EMA, 2004). Furthermore, the agency's commitment to interacting with stakeholders was further maintained and strengthened such as through introducing doctor and patient representatives onto the management board (EMA, 2006) and establishing two patient/consumer and healthcare professionals representatives working parties (the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations and EMA/CHMP Working Group with Healthcare Professionals' Organisations') (EMA, 2006).

However, along the way EMA met several important challenges with implementing its new initiatives (e.g. wider responsibilities, confidentiality issues). Indeed, the difficulties of enhancing transparency, as well as the delays in introducing new policies, contributed to Lönngren's 2010 reflections in *Nature Reviews Drug Discovery* on how transparency had developed at EMA during his leadership. When asked about his biggest regret Lönngren replied:

> *"We could have moved quicker on transparency, but it has not been easy to do so. There are conflicting legislations, and we also need to protect personal data as well as commercially confidential information. If we had been more proactive on this, I would have been happier."* (Mullard, 2010: 912).

While some of these issues concerned confidentiality requirements, others included the challenges of consolidating the agency (EMA, 2007), the consequences of EU enlargement (EMA, 2004, 2007), and the new pharmaceutical legislation, as well as the substantial impacts of bird flu (EMA, 2007) and swine flu (EMA, 2009) on agency operations and especially resource consumption. In other words, although transparency was central to the agency's work, other activities and difficulties slowed down EMA's "step-wise" measures towards greater transparency detailed in its '*Road Map to 2010'*.

Nevertheless, by the end of 2009 EMA released its long-awaited (draft) transparency policy for public consultation (EMA, 2009). This document elaborated on the agency's transparency work and sought to bring together or "reconcile" its previous and future transparency activities into a single coherent policy document (EMA, 2009: 2). This includes clarifying the understanding that transparency is "pivotal" in building trust and confidence in agency operations while fulfilling "the right of EMA stakeholders for impartial and comprehensible information about medicines" (EMA, 2009: 1).

(5.4) EMA comes under fire (2010)

In 2010 the European pharmaceutical transparency landscape changed dramatically. In particular, two main issues emerged. One issue centred on two separate cases brought to the European ombudsman regarding public access to the data that underpins decision-making in EMA's scientific committees. The first case concerns public access to scientific reports on clinical trials, "studies performed to investigate the safety and efficacy of a medicine" (EMA, 2017g)[32]. On 29th June 2007, the Nordic Cochrane Centre applied for access to the full reports (and corresponding protocols) held by EMA for 15 clinical trials relating to two anti-obesity drugs (rimonabant and orlistat) (Gøtzsche and Jørgensen, 2011). The researchers request for

[32] To be clear, clinical trials are scientific studies performed to investigate the safety and efficacy of a medicine in human volunteers (EMA, 2017g). Pharmaceutical companies are required to submit detailed clinical study reports (typically hundreds of pages long) when seeking approval to market a medicine in Europe. Therefore they provide essential information for EMA's scientific committees when coming to an opinion.

documents was first refused by EMA and then by Lönngren himself with both citing commercial confidentiality issues. In a strongly worded letter to Lönngren, the Danish researchers made clear that:

> *"We believe the current lack of openness and transparency in EMA violates basic principles in the EU Treaty and must be changed, as it is also unethical. It is evident that this attitude leads to suboptimal treatment of the patients - and sometimes even to lethal harms - that could have been avoided."* (Jørgensen and Gøtzsche, 2007)

After being refused access, they went on to lodge a complaint with the European ombudsman, which led to a three year and very public dispute between Cochrane and EMA with the ombudsman acting as an independent arbiter (Hampton, 2011). The ombudsman inspected the documents and disagreed with EMA by concluding they did not contain any overriding commercially confidential information (Ombudsman, 2010). On 19th May 2010, the ombudsman provided recommendations in favour of Cochrane:

> *"…the agency gave insufficient reasons for its refusal to grant access […]. Patients' welfare should be given priority over concerns for the commercial interests of the drug industry"* (Diamandouros, 2010 *In*: Bouder *et al*., 2015).

On 31st August 2010 (and after being accused of maladministration), EMA informed the ombudsman it would provide the researchers with the requested documents, which were later received in February 2011 (Gøtzsche and Jørgensen, 2011).

The second case concerned public access to data on suspected adverse drug reactions[33]. In April 2008, an Irish citizen requested access to various EMA 'documents' relating to a medicine used to treat severe forms of acne (Roaccutane). The documents contained details of all suspected adverse reactions made known to the agency since 1982 including so-called serious[34] adverse reactions. Similar to the Cochrane clinical trial case, EMA refused access leading the citizen to complain to the ombudsman via an Irish law firm. EMA argued that (1) EU rules on transparency did not apply to suspected adverse reactions as they are not "documents" *per se*,

[33] An adverse reaction is "a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function" (Directive 2001/83/EC).

[34] A serious adverse reaction is "an adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect" (Directive 2001/83/EC).

(2) providing access "would not benefit citizens because it could result in the circulation of data that could prove to be misleading or unreliable", and (3) making such documents available would result in a "disproportionate" time and administrative resource burden for EMA (ibid, 2010). However, the ombudsman again disagreed with EMA arguing that EU regulations should "apply to requests for all documents held by the agency" (albeit with some exceptions) and that this included suspected serious adverse reaction data (Ombudsman, 2010). In turn, EMA released the documents as requested.

The second event that significantly impacted on EMA occurred when both Lönngren and Vincenzo Salvatore, EMA's chief legal counsel, left the agency with accusations of a 'revolving door' policy at the agency (Makhasvilli and Stephenson, 2013). Although there is debate about the concept, it is generally understood to mean that "agencies tasked with protecting the public come to identify with the regulated industry and protect its interests against that of the public" (Carpenter and Moss, 2013). Shortly after completing his ten years at the helm, Lönngren become an advisor at NDA, a consultancy that advises pharmaceutical companies (Jack, 2011). In June 2012, Vincenzo Salvatore also left the agency and, only a week later, became senior counsel at the Brussels offices of the US-based law firm, Sidley-Austin (Jack, 2012). EMA was accused of not having a sufficient cooling off period for such senior officials. For instance, the Corporate European Observatory (CEO), a corporate lobbying campaign group, stated with regards to Lönngren:

> *"This case is very shocking because of the seniority of the official concerned and the high risk of conflicts of interest. Initially EMA entirely failed to take Lönngren's new consultancy work seriously and to properly consider potential conflicts of interest, until the media raised concerns. Even then, EMA failed to impose a cooling off period or ban on Lönngren undertaking work for consultancy companies, and instead came up with a set of limited conditions* (CEO, 2011).

These two "revolving door" events subsequently had a significant impact on the agency's credibility that should not be underestimated (Makhasvilli and Stephenson, 2013). In particular, they opened the doors to public criticism and demands for more transparency and access to documents at a time when EMA was already under close scrutiny from the ombudsman (*see Lancet*, 2010; Hampton, 2011).

(5.5) The new transparency era (2010-)

In the wake of the ombudsman's recommendations and criticisms of a 'revolving-door' policy, EMA's first reaction was to create a new access to documents policy (EMA, 2010a). The new policy sought to give "wider access than ever before to documents held by the Agency, while ensur[ing] that personal data and commercially confidential information remain[ed] adequately protected" (EMA, 2010b: 17). Notably, the new policy was described as a *'reactive'* approach to transparency as it enabled outsiders to obtain documents held by the agency on request[35]. The new reactive policy symbolised a major change of direction as outsiders could now view much greater quantities of information than ever before (Wieseler *et al*. 2012; Koenig *et al*. 2014) or as Doshi *et al*. (2013: 1) put it: EMA's 2010 access to documents policies "revolutionised the public's ability to access trial data". For example, in 2011 EMA reported that within its first year the new policy increased information requests by 92% and resulted in the release of more than 143 times more pages than in 2010 (EMA, 2011a). Furthermore, while in 2014 alone EMA reactively released 1,816 documents with 167,309 pages (Pott, 2015), in 2015 the agency received 701 requests for access to documents and released 2,972 documents with 333,999 pages.

The second main reaction came in October 2011 when EMA's management board appointed Guido Rasi to replace Thomas Lönngren as its 3rd Executive Director. Rasi had previously dealt with difficult conflict of interest issues and was considered highly suitable for re-building trust in the European agency (Looney, 2012). In particular, he had been a strong advocate of transparency in his previous positon as head of the Italian Medicines Agency (AIFA) after his predecessor, Nello Maritini, along with five drug company lobbyists, had been fired following a six-week suspension in an apparent "drug licenses for cash scandal" (Day, 2008a).

Rasi was immediately faced with several difficult issues. First, the ombudsman's recommendations (on access to documents) and criticisms of a revolving door policy put great pressure on the agency and significantly impacted on its credibility as an independent drug regulator (Makhasvilli and Stephenson, 2013; Bouder *et al*. 2015). Notably, although the ombudsman's recommendations were not legally binding, the rate of compliance among EU

[35] This can be contrasted with a '*proactive*' transparency policy that might involve uploading data onto a publicly accessible web portal (i.e. without needing to request access).

decentralised agencies is consistently high, if not, absolute (Ombudsman, 2010). Second, two safety scandals, involving Mediator and PIP breast implants, had only recently occurred (Looney, 2012). Although member states were the primary targets of blame, the incidents resulted in serious questions about the European public health system and, in turn, increased responsibilities for EMA (especially concerning pharmacovigilance) (Looney, 2012). Third, in May 2011 the European Parliament "refused – by a decision of 637-to-4 to sign off the agency's accounts" (Makhasvilli and Stephenson, 2013: 5). The European Parliament Budget Committee went on to conduct an investigation into EMA's finances as well as its independence from the pharmaceutical industry and demanded that as Looney (2012) put it: "[EMA] self-initiate changes to advance trust through transparency, or it will be imposed". Fourth, shortly after EMA launched its reactive access to documents policy, the pharmaceutical portfolio moved from DG Industry and Enterprise to the Health and Consumer Policy Directorate (DGSANCO), which, according to Löfstedt and Bouder (2014), "is known to favour the interests of patients and consumers over industry". These scandals, incidents, and changes collectively put Rasi in a difficult position early on with outside observers making clear that transparency and trust were "in short supply" (Looney, 2015).

Over the following five years, Rasi made at least three major changes to EMA's transparency strategy. First, the agency began strongly emphasising how it was open to making as much information as possible publicly available. For instance, in Rasi's first annual report he emphasised the sheer quantity of information being made public:

> *"[In 2011,] nowhere was the impact of the agency's much more proactive approach to transparency experienced more dramatically than in relation to the agency's handling of requests for access to documents. During the course of the first full year of operation of the new access-to-documents policy, the agency released more than 1,000,000 pages in response to requests."* (EMA, 2011a).

Rasi also consistently made statements such as "wider public access than ever before" (EMA, 2010b) or "unprecedented levels of access" (EMA, 2014a).

The second major change was the introduction of a remarkable wave of new transparency policies. Many of these expanded the agency's traditional approach such as by further engaging stakeholders and interested parties. For example, workshops were conducted on transparency in 2012 and conflicts of interest in 2013 and five transparency advisory groups were set up in

2013, specifically focused on moving from reactive to more proactive policies (EMA, 2012b, 2013b). The agency also introduced a new database of European experts (EMA, 2011a) and began publishing a list of all new medicines under evaluation by CHMP (EMA, 2012b). Moreover, EMA for the first time began providing much greater operational process transparency of its scientific committees. In particular, scientific committees began publishing its agendas and meeting minutes starting with the Paediatric Committee (PDCO) in 2012 and ending with CHMP by January 2014 (EMA, 2012b, 2014d). In 2013, the regulators made clear:

> *"The starting point for publication of agendas (listing the agenda topics for discussion at the plenary meeting) and minutes of all EMA scientific committees is that everything is transparent"* (EMA, 2013c).

EMA also introduced patient and healthcare professional group representatives into its scientific decision-making for the first time and started discussing the idea of introducing public hearings, a forum where the public are invited to express their views on issues related to the safety of a medicine and guided by a pre-defined set of questions (EMA, 2016c: 2).

Furthermore, in December 2010, the European Parliament and Council adopted new pharmacovigilance legislation that included new transparency requirements (Directive 2010/84/EU; Regulation (EU) No 1235/2010)[36]. In turn, the agency established a new safety assessment and monitoring committee called the Pharmacovigilance Risk Assessment Committee (PRAC), which was viewed as a vehicle for enhancing transparency in itself[37] (EMA, 2012b). It was also required to "operate at a high level of transparency" with meeting minutes being systematically uploaded to EMA's website (ema.europa.eu) starting with its very first meeting in September 2012 (EMA, 2012b).

The third approach, however, received the most attention from outsiders and represented a major change of direction for the agency (Eichler *et al*. 2012, 2013; Bouder *et al*. 2015; Way *et al*. 2016). In particular, EMA introduced several new policies on *proactively* (rather than

[36] EMA (2015a) make clear that the implementation of the 2010 pharmacovigilance legislation in 2012 was strongly influenced by the ombudsman's 2010 recommendations on providing access to suspected adverse reaction data for an Irish citizen (2493/2008/(BB)TS).

[37] Some authors include the creation of institutions and committees in themselves as a way of creating transparency such as by bringing together opaque and fragmented regulatory activities (e.g. Mitchell, 2011: 1882). For example, the European Food Safety Authority was established in 2002 in the wake of the BSE crisis as a way of building public trust *by means* of enhancing transparency in the previously fragmented food safety system (Way and Löfstedt, forthcoming).

reactively) publishing suspected adverse drug reaction and clinical trial data online (i.e. information the ombudsman had recommended EMA make more transparent in 2010) (Way *et al*. 2016). These two policy developments can be addressed in turn.

Following the ombudsman's 2010 recommendations (section 5.4), EMA began providing, for the first time, public access to a sub-set of data on suspected adverse drug reactions proactively from EudraVigilance, "[EMA's] system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the EEA" (EMA, 2017h). In particular, in May 2012 EMA established a publicly accessible and searchable web-portal for viewing such data (adrreports.eu) and, over the following years, incrementally increased the level of access for all stakeholders including patients and healthcare professionals (EMA, 2013b). Appendix D show four example screenshots of adrreports.eu for Deltyba (delamanid), a tuberculosis medicine authorised in 2014. To be clear, EudraVigilance was established in 2001 for the use of pharmaceutical companies, the Commission, EMA and NCAs (e.g. to support the exchange and storage of suspected ADR reports) (Arlett *et al*. 2014; Fouretier *et al*. 2016). EMA began making different levels of information available to various groups in May 2012 and extended this access in September 2014 and December 2015 (EMA, 2017c).

The second and, arguably, most significant change to EMA's policies centred on four distinct levels of clinical trial data transparency (UK House of Commons Science and Technology Committee, 2013) (Table 5.1). The first two are clinical trial registries (level 1) and summary-level clinical trial results (level 2). Clinical trials are (ideally) registered on an online database, which provides a repository of all trials conducted and which includes basic information (level 1). They often contain summary level clinical trial results (e.g. key trial conclusions) (level 2), which are also reported in medical journals (Smith, 2006).

Table 5.1: Table showing four levels of clinical trial transparency. (Source: UK House of Commons Science and Technology Committee, 2013: 34).

Transparency Level	**Description**
Level 1: Clinical trial registration	A record that the trial has been conducted, from a clinical trial register detailing basic trial information

Level 2: Summary-level clinical trial results	A brief summary of the trial's results, together with key conclusions, most commonly in an academic journal or trial register
Level 3: Clinical study report (CSR)	A detailed report, usually prepared for regulatory purposes, of the method, conduct and outcome of a trial, often running to several hundreds or thousands of pages in length
Level 4: Individual patient data	The raw patient data generated over the course of a trial, from which aggregate results and other conclusions are drawn.

EMA had already established an electronic database called EudraCT, which contains information on clinical trials conducted for medicines authorised in the EU, Iceland, Lichtenstein, and Norway (Clinical Trials Directive [2001/20/EC]) (EMA, 2004). The database was not initially intended to provide clinical trial information to the public and healthcare professionals (Egger *et al*. 2013). Rather, it was established as a way of providing national authorities and the Commission with summary and administrative information (Egger, 2013: 458). However, two subsequent EU regulations approved in 2004[38] and 2006[39] stipulated that information and results from the database should be made available to the public (i.e. beyond national regulators and the Commission) (Egger *et al*. 2013). Consequently, in March 2011 EMA launched an online clinical trials register (clinicaltrialsregister.eu), which, for the first time, provided *public* access to a subset of summary clinical trial information from EudraCT (EMA, 2011a; Egger *et al*. 2013). This includes searchable summary results such as the objectives and design of the clinical trial study as well as the main results and conclusions (EMA, 2017g). Furthermore, in July 2014 EMA made it mandatory for trial sponsors to post clinical trial results in EMA's EudraCT database. Hence EMA's clinical trial register seeks to provide the public with summary level information on all clinical trials that have been or are being conducted.

The second two levels of clinical trial transparency are clinical study reports (CSRs) (level 3) and individual patient data (IPD) (level 4) (Table 6.1). They both provide much more granulated levels of data about a clinical trial than registries and summary level trial results.

[38] Article 57(2) of Regulation (EC) No 726/2004
[39] Article 41 of the Paediatric Regulation (EC) No 1901/2006

While full CSRs contain "substantially more information and detail" on a medicine (e.g. the method, conduct and outcome of a trial) and can amount to hundreds or often thousands of pages (level 3) (Doshi *et al*. 2012: 1; Doshi and Jefferson, 2013b)[40], individual patient level data goes further and includes the raw "individual data recorded for each participant in a clinical study" (Riley *et al.* 2010; Koenig *et al*. 2014).

In contrast to levels 1 and 2, EMA's approach to sharing CSRs and patient-level data received the lion's share of attention and criticism from outsiders (*see* Chapter VI for a full discussion). In particular, many different groups took an interest in the agency's policies including those vocally and publicly demanding that EMA enhance transparency. For example, EMA received substantial and continued interest from external researchers (e.g. the Cochrane Collaboration), campaign groups (e.g. AllTrials.net and Sense about Science), a succession of ombudsmen (e.g. Nikiforos Diamandouros and Emily O'Reilly), opinion leaders (e.g. Ben Goldacre), government committees (e.g. the UK House of Commons Science and Technology Committee), scientific committees (e.g. the Institute of Medicine), medical journal editors (e.g. Fiona Godlee and the International Committee of Medical Journal Editors), pharmaceutical companies (e.g. GlaxoSmithKline, Johnson and Johnson, and Pfizer), trade bodies (e.g. PhRMA and EFPIA) and politicians (e.g. Glenis Willmott MEP). Collectively these actors put significant pressure on EMA and its approach to clinical trial transparency[41].

In this heated political context, at least four main milestones in EMA's approach to sharing CSRs and individual patient-level data can be identified. The first major milestone came in April 2012 and notably in the wake of the ombudsman's 2010 decision on clinical trial data. Researchers at the Cochrane Collaboration published an article in *PLoS Medicine* demanding that regulators and industry make full CSRs on the antiviral Tamiflu publicly available:

> *"We challenge industry to either provide open access to clinical study reports or publicly defend their current position on RCT [randomised control trial] secrecy"* (Doshi *et al*. 2012: 2)

The researchers argued that full public access would enable a full independent re-analysis as they contain more detailed information than what is available in published journal articles. In

[40] Specifically EMA (2014b) make clear that clinical reports mean the clinical overviews and clinical summaries and the actual clinical study reports together with appendices to the CSRs.
[41] The arguments for and against different levels of clinical trial transparency are discussed in Chapter VI.

response, EMA regulators agreed that there were clear benefits from making clinical trial data "open to all" (e.g. benefits for public health) but also that there are important challenges and issues that need to be resolved such as patient confidentiality, conflicts of interest with 'independent' re-analyses and misleading results causing public health scares (Eichler *et al*. 2012). The regulators concluded by outlining a "way forward" that included developing standards for personal data protection, ensuring quality standards for re-analyses, and establishing rules of engagement (e.g. requiring researchers to submit a full data analysis plan) (Eichler *et al*. 2012).

The second milestone came in November 2012 when EMA held a workshop on transparency and made clear that it would work towards developing a *proactive* clinical trial transparency policy (EMA, 2012a; Koenig *et al*. 2014). Although EMA would continue to manage a reactive approach on access to documents (i.e. through written requests), the new proactive approach involves uploading data onto a publicly accessible web portal (i.e. without needing to request access). As Rasi announced at the start of the workshop:

> *"Today represents the first step in delivering our vision. We are not here to decide if we will publish clinical-trial data, only how. We need to do this in order to rebuild trust and confidence in the whole system."* (Rasi, 2012).

Workshop delegates went on to discuss issues such as commercial confidentiality, outsiders conducting poor analyses on large datasets and the potential benefits that could be gained from (re)analysing the data (EMA, 2012a; Way *et al*. 2016). In the following year, the agency established five advisory groups on topics of concern coming from the workshop and conducted a three month public consultation on its proactive policy that generated over 1,000 comments from over 150 individuals and organisations.

The third milestone came in October 2013 when EMA regulators published a perspective article in the *New England Journal of Medicine*, titled "*Access to Patient-Level Trial Data – A Boon to Drug Developers*" (Eichler *et al*. 2013). Whereas previously the agency was clear to emphasise concerns over proactively publishing CSRs (e.g. patient confidentiality and the misuse of data), the regulators set out detailed arguments explaining the expected benefits for the biopharmaceutical industry:

> *"It is ironic that the organizations that most resist wider access to data are the ones that stand to benefit so much from greater transparency"* (Eichler *et al*. 2013: 1579).

One contributory reason for the regulators' article centred on their frustration over being sued by two pharmaceutical companies, AbbVie and InterMune, over reactively releasing several CSRs. Although the regulators ended up settling outside of court, a clear legal definition of commercial confidentiality was not agreed upon, which kept the door wide open for future cases.

The fourth major milestone came on 2nd October 2014. After four years and a long consultation period (Koenig *et al.* 2014), EMA announced its final proactive CSRs policy (EMA, 2014a, 2014b). The "landmark" policy would mean that, starting in January 2015, all clinical reports submitted to the agency by pharmaceutical companies would be published on an online database (EMA, 2014b; Löfstedt *et al*. 2015). In other words, 'outsiders' would be provided with unprecedented levels of access to the data and information that underpins decision-making in it scientific committees. On Christmas Day 2014, EMA regulators went on to explain the rationale behind its policy in the *New England Journal of Medicine* (Bonini *et al*. 2014) and subsequently published a question and answer document in 2015. The final policy also made a clear distinction between the sharing of CSRs and individual patient level data. In particular, the agency specified that further debate on the sharing of individual patient level data would be undertaken after an extended public consultation period (mainly due to patient anonymisation and de-identification challenges) (*see* Koenig *et al*. 2014). Overall, this fourth milestone symbolised a major change of direction from 2009 when EMA argued that information could not be made publicly available for commercial confidentiality reasons and hence signified the agency's full entry into the new transparency era.

Chapter VI: EMA's INPUT TRANSPARENCY POLICIES

The historical analysis showed that between 2010 and 2016 EMA's transparency strategy changed significantly (Chapter V). After introducing a new *reactive* access to documents policy in 2010, the agency went on to develop several new policies that centred on the *proactive* publication of the data and information that underpins decision-making in its scientific committees online. This was a major change of direction for EMA partly because the regulators began focusing on enhancing the transparency of scientific committee *inputs*, a transparency object largely omitted from its previous strategy.

However, what the chapter did not provide was an explicit discussion of the goals and connected audiences of EMA's most recent proactive input policies (Chapter II). For example, a discussion was not provided on the goals of enabling external researchers to re-use scientific committee data or empowering patients to make more informed medical decisions. Chapter V also did not place each of EMA's proactive transparency policies within its broader context. For example, many other organisations have sought to enhance the transparency of scientific data used to inform decision-making such as the US FDA or World Health Organisation (WHO). What is needed now is an in-depth examination of the goals and audiences of EMA's proactive transparency policies contextualised around wider efforts to enhance transparency in the pharmaceutical policy domain.

This chapter examines the three main informational input transparency policies in-depth (i.e. the three embedded sub-units of analysis):

1. Establishing an online clinical trials register called EU-CTR (clinicaltrialsregister.eu);
2. Publishing summary-level clinical trial results on EU-CTR;
3. Publishing clinical study reports online (clinicaldata.ema.europa.eu);

To be clear the main purpose of the chapter is to display the case study evidence on each of these policies. A full evaluation of EMA's input transparency is provided in Chapter VIII.

The chapter is structured as follows. Clinical trials are first explained. All three policies are then discussed in turn contextualised around the broader pharmaceutical transparency context

(i.e. placing EMA's policies among other related developments). In each section the goals and related audiences of each policy are examined. An understanding and analysis of the most significant developments and issues of each policy are then provided. Overall, the chapter shows that, although much discussion has focused on the impacts on external researchers and industry, there is little to no understanding of the perspectives of patients and medical doctors. The chapter will thus provide a point of departure for the third empirical chapter of this thesis (Chapter VII).

(6.1) Clinical trial data

Since 2010, EMA has focused on enhancing the transparency of data on clinical trials, "studies performed to investigate the safety or efficacy of a medicine" (EMA, 2017g). Clinical trials are essential for the drug licensing process as they provide detailed information on the safety and efficacy of a medicine pre-authorisation. In particular, randomised clinical trials, studies where "the subjects are randomly distributed into groups which are either subjected to the experimental procedure (as use of a drug) or which serve as controls" (Merriam-Webster, 2016), are often considered the most rigorous way of testing the cause-effect relation between a medicine and its outcome (Sibbald and Roland, 1998; Hulley *et al*. 2013). Clinical trials can also be conducted post-authorisation in what EMA describe as post-authorisation safety studies. These studies are conducted to obtain further information on a medicine's safety or to measure the effectiveness of various risk-management measures (e.g. preventing incorrect use) (EMA, 2017g). Crucially, EMA's scientific committees – including CHMP and PRAC – rely on clinical trial data to inform evidence-based medical decision-making. For example, while CHMP analyse clinical trial data submitted by pharmaceutical companies applying for a marketing authorisation, PRAC are responsible for assessing the results of post-authorisation safety studies including post-authorisation clinical trials.

(6.2) Clinical trial registration

The first level of clinical trial transparency is registration (Chapter V) (Science and Technology Committee, 2013: 34). Clinical trial registers provide a record of authorised, on-going and completed trials. They typically include basic scientific and administrative information such as the medical condition being studied, a unique identifier number and contact details for

obtaining additional information (Dickersin and Rennie, 2003; Ghershi and Pang, 2009). In March 2011, EMA launched its own publicly accessible online register called EU-CTR (clinicaltrialsregister.eu) (EMA, 2011b). The register provides public access to a sub-set of information from EudraCT, EMA's clinical trial database, on trials conducted in the EEA and EU member states (Egger *et al*. 2013), as well as certain trials conducted outside the EU/EEA (EMA, 2011b). Each record includes information on the design of the trial, the name of the sponsor, the investigational medicine, the therapeutic area, and its status (e.g. authorised, on-going or complete) (EMA, 2017i). Figure 6.1 provides a screenshot of one such record in EU-CTR, which examined "the effect of Thalidomide on sputum biomarkers in idiopathic pulmonary fibrosis cough". To be clear, EMA's register also contains summary-level results (level 2) but this is addressed separately in section 6.3.

EudraCT Number: 2010-023828-24 **Sponsor Protocol Number:** 09107	**Start Date*:** 2011-06-09
Sponsor Name: University of Nottingham	
Full Title: The effect of Thalidomide on sputum biomarkers in IPF cough.	
Medical condition: Cough in Idiopathic Pulmonary fibrosis.	
Disease:	
Population Age: Adults, Elderly	**Gender:** Male, Female
Trial protocol: GB *(Prematurely Ended)*	
Trial results: *(No results available)*	

Figure 6.1: Screenshot providing an example of a clinical trial record in EMA's register (clinicaltrialsregister.eu). 27/07/2016. Note: the trial protocol can be accessed (on the website) by clicking the blue 'GB' symbol. Source EMA (2017i)

Clinical trial registration is neither new nor limited to EMA's EU-CTR. One of the first searchable and computerised international registers, developed by the US National Institute of Mental Health, and which focused on psychopharmalogical agents, was launched in 1967 (Disckersin and Rennie, 2003). A multiplicity of registers has since been created across the world including in the United States (ClinicalTrials.gov), Japan (Japan Primary Registries Network), China (Chinese Clinical Trials Registry), Thailand (Thai Clinical Trials Registry), South Korea (Clinical Research Information Service), Cuba (Cuban Public Registry of Clinical Trials), and many others (Zarin *et al*. 2015; WHO, 2017). Several speciality and regional registers have also been created (Dickersin and Rennie, 2003). For example, TrialsCentral

seeks to bring together all US registers onto one searchable web portal (Dickersin and Rennie, 2003). As of 3rd August 2016, the FDA had the largest international register in the world (ClinicalTrials.gov) with over 221,602 studies registered from all 50 states and 192 countries[42]. In comparison, EMA's register contained 47,090 trials[43] (EMA, 2017i). EMA's register therefore contributes to a global network of trial registers that have sought to increase clinical trial registration transparency since at least the 1960s (Dickersin and Rennie, 2003; Egger *et al*. 2013).

EMA's EU-CTR is also recognised as one of the WHO's fourteen *primary* registries. Records in these primary registries are uploaded weekly onto the WHO's International Clinical Trials Registry Platform (ICTRP), which seeks to bring together trial registration data onto a single point of access (Viergever and Li, 2015). All fourteen of these registries have to meet specific requirements (e.g. on content, quality, validity, and accessibility), which were agreed upon by the International Committee of Medical Journal Editors (ICMJE) (Angelis *et al*. 2004). WHO's platform now contains one of the largest repositories of clinical trial records in the world. Therefore EMA plays a significant part in clinical trial registration especially considering EU-CTR is also one of the largest contributors to WHO's register (Viergever and Li, 2015),

(6.2.1) Goals and audiences for level 1

Trial registration is almost universally regarded as highly beneficial (Antes and Chalmers, 2003; Angelis *et al*. 2004). For example, witnesses contributing to a prominent Science and Technology Committee report (2013) representing various groups (e.g. industry, regulation, the medical community and NGOs), unanimously gave support for trial registration transparency. The report went on to recommend that the UK government takes steps "to ensure that […] all clinical trials conducted in the UK, and all trials related to treatments used by the NHS are registered in a WHO-listed primary registry" (Science and Technology Committee, 2013). Although there is disagreement over what can ultimately be achieved with registers, at least four main goals have been prominently discussed in the medical literature, which can each be connected to specific audiences (Table 6.1). To be sure, although many different groups

[42] See https://clinicaltrials.gov/ for updated figures.
[43] See https://www.clinicaltrialsregister.eu/ctr-search/search for updated figures

might benefit from trial registration, the audiences of transparency are those individuals, groups, and institutions that are expected to actually use a clinical trial register (Chapter II).

Table 6.1: Four main goals and audiences of clinical trial registration

Goals	Target Audiences
To better connect trialists with patients and hence speed up recruitment and drug discovery	Patients and their doctors
To provide a way of finding out what trials have been conducted, where, and by whom	Trialists and medical researchers
To minimise scientific issues with a trial before (e.g. its design) and after (e.g. post hoc hypothesis testing) it has been conducted	Medical reviewers and researchers
To help medical researchers obtain trial results (e.g. by contacting trialists)	Medical researchers (e.g. systematic reviewers)

One goal of registration is to provide patients wishing to participate in a clinical trial, and their doctors, with a way of finding out about recruitment opportunities (Table 6.1) (Dickersin and Rennie, 2001). For example, they can search an online register to identify trials that are recruiting patients with relevant medical conditions. In turn, connecting patients with trial recruiters seeks to speed up drug discovery and improve the clinical trial process through efficiency improvements (Antes and Chalmers, 2003; Ionnadis *et al*. 2014). For example, Dickersin and Rennie (2003) comment that one early argument for trial registration was to speed up a "cure for cancer" by making it easier for doctors and patients to find out which trials are recruiting (Hubbard and DeVita, 1987). Registers have great potential for providing recruitment information (Hudson and Collins, 2015) with the FDA's register receiving an average of 207 million page views per month and 65,000 unique visitors daily as of October 2015[44]. Indeed, encouraging patients to participate in clinical trials and making it easier for them to enrol is a highly desirable and on-going goal for the progression of medical research (Heywood *et al.* 2015).

[44] Comparative data on EU-CTR were not available.

A second goal is to provide people who are intimately involved in a trial (hereafter 'trialists') as well as medical reviewers (e.g. individuals on ethical review boards or health technology assessors) with a way of knowing about authorised, on-going, and completed trials (Table 6.1). As Viergever and Li (2015: 8) put it, they can find out "what clinical trial research is being conducted, where it is being conducted, by whom and how". Vice versa, if trials are not registered then it can be difficult, if not impossible, to reliably identify all trials by other means such as by searching medical journals or conference abstracts (Institute of Medicine, 2015; Dickersin and Rennie, 2003). For trialists, studies found in registers can inform future designs and hence increase the value of research. This is also expected to help prevent the unnecessary duplication of research effort and thus enable trial sponsors to put resources into other study designs or activities (Siontis *et al*. 2013; Moher *et al*. 2014; Chan *et al*. 2014). For reviewers, registers can inform decision-making (e.g. whether a trial should be approved or not) by providing an understanding of what similar work relevant to a proposed new trial exists (Laine *et al*. 2007). Registers are therefore expected to provide many benefits for the scientific clinical trial process and drug discovery (Chan *et al*. 2014; Moher *et al*. 2014; Institute of Medicine, 2015).

A third goal is to enable medical reviewers and researchers to identify issues with trials both before and after they have been performed (Table 6.1) (Rottingen *et al*. 2013; Viergever *et al*. 2013). Crucially, many registers require the *prospective* inclusion of study protocols, "a detailed account of the hypothesis, rationale and methodology" of a clinical trial (Godlee, 2001). Before trials are conducted, protocols can enable reviewers and researchers to identify issues early in the process and offer suggestions for improvement (e.g. how to improve study designs) (Godlee, 2001). After trial completion, prospectively recorded protocols can be compared with the results reported by investigators (e.g. in medical journals). Medical reviewers and researchers can therefore identify discrepancies between what trialists planned to do and what was actually done and reportedly found. This is expected to help minimise issues such as selective reporting, unreported outcomes, and post hoc amendments, three issues that are known to create biases in the published medical literature (Lumey, 2001, Ioannidis, 2005; Song *et al*. 2010; Ross *et al*. 2012). For example, 'data dredging' occurs when trialists mine through data to find statistically significant trends rather than test a hypothesis detailed in the original protocol (Lumey, 2001; Ioannidis, 2005; Ross *et al*. 2012). Others have also

argued that trialists would be deterred from activities such as selective reporting if protocols are recorded in trial registers prospectively (Chan *et al*. 2004; Jones *et al*. 2013).

A fourth goal is to enable medical researchers (e.g. systematic reviewers) with a way of identifying and obtaining unreported trial results (e.g. by using contact details found in registers) (Table 6.1). Past studies have shown that many trials are never published in medical journals with some estimates of around 50% of completed trials having unreported results (Turner *et al*. 2008; Vedula *et al*. 2009; Chan *et al*. 2014; Ioannidis *et al*. 2014). If trials are prospectively registered then medical researchers can monitor whether the results have been published and chase up trialists that have not done so (Chalmers, 2006; McGee *et al*. 2011; Chalmers *et al*. 2013). For example, one of the first studies examining trial registration (Simes, 1986) used a registry of cancer trials – the International Cancer Research Data Bank – to obtain unreported trial results from the original investigators via letter. Trial registration and summary level results reporting can therefore have a complementary relationship or, as Jones *et al*. (2013: 2) put it:

> *"…trial registration can increase awareness of possible publication bias within the medical literature by allowing the public to compare the subset of trials with published results to the total number of trials that were registered and conducted".*

Therefore trial registration seeks to contribute towards mitigating the selective reporting of trial results in the medical literature, an issue discussed in more detail in section 6.3.

(6.2.2) Tackling non-compliance

Despite almost universal agreement that trial registration has important benefits, there are several issues that limit their effectiveness. All of these issues are relevant to EMA's register. Some concern registers themselves such as issues with their searchability and the need to bring all databases together (Glanville *et al*. 2014; Viergever and Li, 2015). However, two of the most significant issues centre on non-compliance. The first non-compliance issue is that many studies have collectively shown that around 40% of published trials – such as those found in medical journals and conference abstracts – have never been registered (Song *et al*. 2010; McGee *et al*. 2011; de Wetering *et al*. 2012; Freshwater *et al*. 2013; Vivergener and Li, 2015; Miller *et al*. 2015). For example, van de Wetering *et al*. (2012) examined a sample of

publications on MEDLINE, one of the largest databases of abstracts and citations in the medical field, and found that 39% of published randomised clinical trials had not been registered[45]. There is therefore clear evidence that registers do not provide a full record of all trials conducted.

The second non-compliance issue is that many trials that have been registered are recorded poorly. In particular, several studies have shown that records can be inaccurate (e.g. incorrect information), incomplete (e.g. missing protocols), not up-to-date, or contain trials that were registered retrospectively (rather than prospectively) (Viergever *et al*. 2014; Viergever and Ghershi, 2011; Piffner *et al*. 2014). For example, Viergever and Li (2015) found that 48% of trials registered in 2012 had been done so retrospectively. These data quality issues present a significant problem as most of the aforementioned goals cannot be achieved without accurate, complete and prospective registration (Simes, 1986). For example, the goals of connecting patients with recruiters, enabling reviewers to search for trials (e.g. to inform decision-making), minimising selective reporting, and enabling researchers to chase up study results require high quality and accurate records.

In seeking to address non-compliance issues in particular, several major developments have occurred since the late 1990s (Chalmers, 2006). Many of these have been influential including self-regulation at universities, requiring registration as a condition of ethical approval, and enforcement of registration by funders (*see* Viergever and Li, 2015 for a discussion; Bian and Wu, 2010; Chalmers, 2013). However, three frequently cited milestones have been particularly significant in improving registration rates. First, legislation has been passed in both the US and EU to make trial registration a legal obligation for most trials (Weber *et al*. 2015). In the US, the FDA Modernisation Act of 1997 introduced the requirement that all trials "for serious or life threatening conditions" must be registered on ClinicalTrials.gov (Zarin *et al*. 2005, 2011, 2015). More recently, and following the passing of the FDA Amendments Act of 2007, more types of trials were required to be recorded on FDA's register. The agency also gained the power to give monetary penalties of up to $10,000 a day for non-compliance (Zarin *et al*. 2005, 2011, 2015). This led, in the following year, to annual registration rates in North America rising to its highest level (Viergever and Li, 2015).

[45] Indeed, this figure does not include clinical trials that were never published in medical journals or not indexed on MEDLINE.

Second, many medical journal editors have made it mandatory for trials to be prospectively registered in order even to be considered for publication. Most notably, in 2005 the ICMJE introduced the requirement that "all clinical trials must be registered at a clinical trial registry to be eligible for publication" (Viergever and Li, 2015: 2; Angelis *et al*. 2004; Zarin *et al*. 2005; Laine *et al*. 2007; van de Wetering *et al*. 2012). This is important as the ICMJE have eleven major biomedical journal members including the 'big five'[46] and a large number of non-member journals that follow their requirements (ICJME, 2017). Indeed, several authors have argued that ICMJE's requirements have been one of the most successful ways of improving registration rates (Song *et al*. 2010; Zarin *et al*. 2015; Vivegever and Li, 2015).

Third, several international organisations have made strong declarations to encourage trial registration. In particular, in 2008 the World Medical Association amended the declaration of Helsinki, a set of ethical principles regarding human experimentation, to include two new principles, which made clinical trial registration an ethical obligation (Zarin *et al*. 2015). The most relevant paragraph, modified in 2013, states:

> *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject"* (World Medical Association, 2013).

Elevating clinical trial registration to an ethical obligation is significant considering the Helsinki declaration is widely considered in the medical community to be the "cornerstone document for human research ethics" (Shrestha, 2012: 256).

Several studies have shown that these developments and others have significantly increased at least the number or quantity of trials registered (Figure 6.1) (Reveiz *et al*. 2007; van de Wetering *et al*. 2012; Zarin *et al*. 2015; Viergever and Li, 2015). For example, Viergever and Li (2015) analysed clinical trial registration rates in WHO's registry network platform (ICTRP) since the ICMJE's journal publication criteria were announced in 2004 (Angelis *et al*. 2004). The study found that registration greatly increased in the ICTRP from 3,294 *annual* trials registered in 2004 to 23,385 in 2013. The sharpest rise was also between 2004 and 2005 when

[46] These are *the Lancet*, *Annals of Internal Medicine, the British Medical Journal* (BMJ), *the New England Journal of Medicine* (NEJM*)* and *the Journal of the American Medical Association* (JAMA).

ICMJE introduced its new requirements (Angelis *et al.* 2004; Viergever and Li, 2015). Similarly, Zarin *et al*. (2015) chart a significant cumulative increase in the number of registered trials in ClinicalTrials.gov since its creation in February 2000 until September 2014. The analysis also found that the most substantial increase in registration rates came after the ICMJE's new requirements were announced in 2004. In other words, both studies show that the ICMJE's requirement of making registration a criteria of publication significantly and notably increased registration rates.

Despite these improvements, there remain significant issues with non-compliance. Although Viergever and Li (2015) found that registration rates increased five-fold globally between 2004 and 2013, the study also found that these improvements did not occur equally in all parts of the world. For example, improvements in registration rates have been more gradual in Asia. The study also found that many studies were registered retrospectively during this period, which strongly impacts on the usefulness of trial registers to achieve any of the four main goals. For example, issues with selective reporting and post hoc hypothesis testing cannot be addressed. Another recent study (Miller *et al*. 2015) provided a cross-sectional analysis of all clinical trials submitted to the FDA for approval in 2012 that were sponsored by pharmaceutical companies. The study found that out of 15 drugs sponsored by industry that had a total of 318 relevant trials, a median of 57% of trials were registered per drug (i.e. 43% of trials were not registered) (Miller *et al*. 2015). Thus these studies provide further evidence that non-compliance with trial registration remains a significant issue.

Considering trial registration has become a legal and ethical obligation in many countries across the world, it would seem perhaps surprising that registration rates are not significantly higher. One issue has centred on legal requirements. Some authors have pointed out that there has been a lack of enforcement. For example, although FDA have the power to fine up to $10,000 a day they have never done so and their powers only reach to US-based trials. Others have argued that there has been a lack of applicability in the law across different jurisdictions. For example, although new laws have been introduced across the world such as in Europe, the US, Canada, Argentina, Brazil, India, Israel and South Africa, the majority of low and middle income countries have not introduced legislation on clinical trial registration.

A second issue is that there has been a lack of widespread implementation of some of the most successful initiatives (Bian and Wu, 2010). The ICJME's requirements have been one of the most successful initiatives to date to improve trial registration. However, only 30% of English language journals actually require registration and many of those that do require registration do not check for compliance (Wager and Williams, 2013). Other successful initiatives such as mandating registration as a condition for ethical approval has also lacked widespread implementation (Bian and Wu, 2010).

A third issue is that there have been technical and resource-based difficulties for trialists. For example, editors at the BMJ have asked why some trialists seeking publication have not registered trials prospectively (Weber *et al*. 2015). Responses from researchers include unclear responsibilities among trialists (e.g. principal investigators assuming others will register a trial) or that registration is overly burdensome (e.g. lack of resources for non-industry sponsored studies) (Weber *et al*. 2015). For example, one large foundation was asked why they did not register their trial and responded:

> *"[The reason to require registration is] mainly to stop drug companies. [The principal investigator] is a developing country scientist doing this important study alongside a very busy job. Drug companies have whole departments devoted to compliance with regulations and processes like this"* (Weber *et al*. 2015).

There are also many other local and regional issues that have led to reducing the impact of legal and ethical obligations to enhance clinical trial transparency (Bian and Wu, 2010; Vivergener and Li, 2015; Miller *et al*. 2015; Weber *et al*. 2015).

(6.3) Summary-level trial results

The second level of clinical trial transparency is the reporting of summary-level results (level 2). Summary results refer to the "relatively basic information needed to understand the outcome and potential implications of a clinical trial" (Science and Technology Committee, 2013: 36). They typically include an explanation of its aims, methods, results, and statistical findings (ibid, 2013). In other words, they go beyond the basic administration information prospectively recorded in a register to include information on the outcomes of a completed trial. Although summary results can also be found in conference abstracts, working papers, dissertations, and reports (Song *et al*. 2010), they are more formally reported in medical journals (e.g. one of the

big five) and, more recently, registers (e.g. EU-CTR or ClinicalTrials.gov) (EMA, 2013d, Zarin *et al*. 2015). Appendix E provides an example of one such summary-level record for a vaccine trial that ended in 2007 and was first reported in EU-CTR in 2014. The record is 16 pages long and includes an identification number as well as details on subject dispositions, baseline characteristics, end points, adverse events, and others.

Medical journals have historically been the primary mode of disseminating summary-level trial results and are used by various audiences (Hagdrup *et al*. 1998; Craig *et al*. 2001; Dickersin and Rennie, 2003; Turner *et al*. 2008; Chan *et al*. 2014). This includes medical researchers, policy and healthcare decision-makers, and medical doctors as well as trial participants and some patients. However, over the past few decades trial registers have increasingly been used as a mode of disseminating summary results. In particular, EMA and FDA have mandated that the results of certain trials are reported in EU-CTR or ClinicalTrials.gov, respectively (FDA Amendments Act, 2007; EMA, 2014d).

After establishing a publicly accessible online register in 2011 (see section 6.2), EMA subsequently began encouraging trial sponsors to *voluntarily* upload summary results onto EudraCT in 2013. In so doing, outsiders could access the results of trials voluntarily recorded on EU-CTR via the EU-CTR web-portal (clinicaltrialsregister.eu). In July 2014, EMA made it *mandatory* for sponsors to post results in EudraCT either six months or one year after trial completion or premature termination (Clinical Trial Directive 2001/20/EC; EMA, 2014d). Recent EU clinical trial regulations go further by requiring that trial sponsors upload a results summary for medical experts within one year of trial completion and an additional summary written in 'plain language' for 'laypersons' (Clinical Trial Regulation EU no. 536/2014) (Abou-El-Enein and Schneider, 2016). Therefore the new regulation as well as other initiatives introduced by EMA (and the Commission) seek to enhance the transparency of summary level results for both expert and lay audiences, although 'layperson' summaries were still under consultation when this thesis was being finalised (*see* Health Research Authority, 2016).

(6.3.1) Goals and audiences for level 2

The overriding reason for mandating that results are reported in registers centres on several issues with medical journals as a mode of dissemination. In particular, registers primarily seek

to overcome important limitations associated with medical journals that have resulted in the 'invisibility' of trial findings in the published literature (Song *et al*. 2010). There are at least five main goals of reporting results in registers, including EMA's EU-CTR, that seek to overcome these issues (Table 6.2).

Table 6.2: Five main goals and connected audiences of summary-level results reporting

Goals	Target Audiences
Nonpublication: To improve issues of publication bias	Medical researchers
Nonpublication: To improve the timeliness of trial reporting	Medical researchers
Nonpublication: To improve outcome reporting	Medical researchers
To provide a structured and standardised format for reporting results	All users of trial results
To inform participants, medicine-users, and healthcare professionals about the results of clinical trials	Trial participants, patients, and healthcare professionals

The overriding goal of register reporting is to improve the issue of nonpublication in medical journals (Table 6.2) (Chan *et al*. 2014; Zarin *et al*. 2015). A key advantage of trial registers, as a mode of results dissemination, is that they enable regulators to mandate publication (e.g. through legal requirements and powers to fine trialists) (EMA, 2014d; Zarin *et al*. 2015). This is important because, since at least the 1970s (e.g. Rosenthal, 1979), numerous studies have shown that the results of many trials are never reported in medical journals even many years after study completion (Turner *et al*. 2008; Song *et al*. 2000, 2010; Dwan *et al*. 2008, 2013; Schmucker *et al*. 2014; Chan *et al*. 2014). This includes a range of trial types including adult and paediatric populations, with under-reporting rates predominately ranging between 25% and 45% (Pica and Bourgeois, 2016). For example, Jones *et al*. (2013) found that out of 585 completed trials, prospectively registered on ClinicalTrials.gov and all of which included at least 500 participants, 171 (29%) had not been published in any medical journal surveyed. Medical journals therefore suffer from under-reporting and, as Hudson and Collins (2015: 355) put it:

> *"Other means to share [trial] data are necessary because of both real and potential harm can result from failure to fully disclose the results of clinical trials".*

This means that EMA and FDA seek to improve the dissemination of trial results through mandating results reporting in EU-CTR or ClinicalTrials.gov, respectively.

Following this nonpublication issue, the first main goal of reporting summary results in trial registers is to increase the reporting of both negative and positive trial results (Table 6.2) (Dickersin, 1997; Song *et al*. 2010). Along with improving reporting in general, a key advantage of trial registers is that (1) it is free to upload results and (2) decisions to report are expected note to be significantly influenced by the nature or direction of the trial's results (e.g. whether results support the investigated medicine or not). This is viewed as a key advantage of registers as many studies examining reporting rates have shown that medical journal non-publication is strongly linked to *publication bias*, "the publication or non-publication of research findings, depending on the nature and direction of the results" (Sterne *et al*. 2011: 2). There is strong evidence – both direct (e.g. cohort studies of proposals submitted to review boards) and indirect (e.g. surveys of published results) – that trials with statistically significant or positive results are more likely to be published in medical journals than those with statistically insignificant or negative results (Dwan *et al*. 2008, 2013; Song *et al*. 2000, 2010; Chan *et al*. 2014; Dickersin, 1997; Turner *et al*. 2008; Manzoli *et al*. 2014). An updated 2012 systematic review, for example, found that positive results were more likely to be published in medical journals than negative results in all fifteen recent studies examined (Dwan *et al*. 2008, 2013). There is also evidence that industry are more likely to publish positive rather than negative results leading to questions of conflicts of interest in the medical literature (Naci and Ioannidis, 2015). EMA's register therefore seeks to improve the dissemination of both positive and negative results through mandating register reporting regardless of the results.

A second main goal of registers is to improve the timeliness of trial reporting (Table 6.2). Register reporting seeks to ensure that trial results are published without delay regardless of whether they are positive or negative. An important advantage is that the regulators (or medical researchers) can monitor how quickly or slowly a trial sponsor or principal investigator publishes results after study completion. This is because, in Europe and the US, trials are required to be registered prospectively (that is, before recruiting the first participant) and with a stated date of completion. This is particularly important because many studies have shown that medical journals suffer from *time-lag bias*, "the rapid or delayed publication of research findings, depending on the nature and direction of the results" (Sterne *et al*. 2011: 2). Since

Ioannadis (1998) first raised the issue, a strong evidence base has shown that trials with positive results are likely to be published more rapidly than those with negative results (Ioannidis, 2001; Trikalinos *et al*. 2004; Decullier *et al*. 2005; Scherer *et al*. 2007; Hopewell *et al*. 2007; Manzoli *et al*. 2014; Chen *et al*. 2016). For example, Hopewell (2007) found that on average positive results are published approximately 2-3 years earlier than trials with negative results. This time-lag bias can significantly affect medical decision-making. For example, Manzoli *et al*. (2014) argue that delays in reporting vaccine trial results during an epidemic can distort the evidence needed for recommendations, allocation of resources, stockpiling of medicines, and other public health action. Therefore EMA seeks to mitigate time-lag bias through mandating that results are reported in trial registers within pre-defined time frames, which is typically 6 months to 1 year after study completion but varies between trials.

A third main goal of register reporting is to ensure that all trial outcomes are published regardless of whether they have positive or negative results (Table 6.2). A key advantage of reporting results, at the place a trial was registered (i.e. with the original registration information), is that the regulators are able to request that trialists include information on all outcomes included in the trial protocol (assuming the protocol was prospectively registered). This is important because many studies have found that medical journals suffer from *outcome-reporting bias*, "the selective reporting of some outcomes but not others, depending on the nature and direction of the results" (Sterne *et al*. 2011: 2; Chan *et al*. 2004; Dwan *et al*. 2008, 2013). There is strong evidence that positive outcomes are more likely to be exaggerated and negative outcomes are less likely to be reported altogether (Saquib *et al*. 2013; Jones *et al*. 2013; Roasti *et al*. 2016; Ioannidis *et al*. 2017). For example, while one review found that statistically significant outcomes were more likely to be completely reported than non-significant outcomes (Dwan *et al*. 2013), another found that there is large diversity "on whether and how analyses of primary outcomes are adjusted in randomised control trials" (Saquib *et al*. 2013). Furthermore, when results are reported at the place of registration there is a complementary relationship between registering trials prospectively and mitigating outcome reporting bias (section 6.2). For example, medical researchers can identify when trials were originally registered, what outcomes were supposed to be reported, and what outcomes were actually reported. Therefore EMA seeks to mitigate outcome-reporting bias such as by requesting further information from trialists relating to unreported outcomes.

By mandating that results are reported in registers, whether they are positive or negative, the regulators, in turn, seek to achieve several secondary goals. First, register reporting seeks to reduce the wastage of scientific resources (Chan *et al*. 2014). If results, and especially negative results, are not reported then trialists may unnecessarily repeat a trial that is doomed to fail (Chalmers *et al*. 2014). Others have argued that there would be better resource allocation for clinical trials, less redundant research conducted (e.g. duplicating trial results), less research that is 'misguided' and better prioritisation of research questions and study designs (Chan *et al*. 2014). Rottingen *et al*. (2013) estimate that 240 billion US dollars are wasted annually due to non-publication. Chalmers and Glasiou (2009) argue that around 85% of research investment is wasted for various reasons and better summary level results transparency is expected to contribute towards solving this issue. Trial register reporting is therefore expected to help tackle non-publication and associated biases, which can significantly waste scientific resources (Chalmers *et al*. 2014; Ioannadis *et al*. 2014).

Second, register reporting seeks to reduce unnecessary harm to participants (Zarin and Tse, 2008; Gabler *et al*. 2012; Chan *et al*. 2014; Farrar *et al*. 2014; Ventetuolo *et al*. 2014; Institute of Medicine, 2015). Many authors have argued that if terminated trials or negative results are not published then participants can be harmed (*see* Hwang *et al*. 2016 for a discussion). For example, numerous actors point to a failed phase 1 trial conducted in 2006 at Northwick Park Hospital in London (Zarin and Tse, 2008). The trial was on a super-monoclonal antibody called TGN1412 and caused "catastrophic multisystem failure" for eight healthy volunteers (Goodyear, 2006). Arguably the incident could have been avoided if the results of a similar study, taking place over a decade earlier, were made available to the investigators (Goodyear, 2006). Some have gone further arguing that this also applies to failed phase 3 clinical trials, which can inform "clinical practice, regulatory decisions and future research" including study designs that are less likely to harm future participants (Hwang *et al*. 2016).

Third, register reporting seeks to facilitate and improve systematic reviews and other analyses of the literature. A key issue with non-publication is that systematic literature reviews, that many consider as the 'gold standard' for scientific research on the safety and efficacy of medicines (Dickersin and Rennie, 2003; Doshi *et al*. 2012), rely on analysing both positive and negative results. If trials with negative results are less likely to be disseminated in medical journals, then researchers can identify spurious beneficial effects of a medicine or miss

important adverse events (Sterne *et al*. 2011). In turn, decision-makers that rely on systematic reviews – such as medical doctors and health technology assessors – may make ill-informed decisions (Whittington *et al*. 2004; Kyzas *et al*. 2005; Sterne *et al*. 2011). As Turner *et al*. (2008: 253) put it: non-publication can "result in unrealistic estimates of drug effectiveness and alter the apparent benefit-risk balance".

Beyond issues with non-publication and associated biases, a fourth main goal of register reporting is to provide a standardised and structured format for reporting trial results (Table 6.2) (Altman, 2015). Indeed, EMA's register provides such a standardised and structured format (*see* Appendix E) (EMA, 2017i). This is expected to provide benefits such as trialists avoiding missing important information through standardisation and medical researchers being able to find key methodological details (Altman, 2015):

> *"...using templates and mandatory reporting of some elements may facilitate the work of researchers by reminding them what they need to report and by standardising their reporting"* (Riveros *et al*. 2013)

This is important as there is evidence that trials can be reported poorly in medical journals and that key information can be excluded unintentionally and left unidentified by peer-reviewers (Wharton, 2015; Weissgerber *et al*. 2016). Standardisation in trial registers is expected to better aid researchers in interpreting results and designing future studies. For example, some have argued that results reported in trial registers are more complete than in journal articles (Riveros *et al*. 2013; Hartung *et al*. 2014), although this has been strongly contested (Manzoli *et al*. 2014: 5). Nevertheless, EMA's register has the ability to standardise results reporting in a more structured format than is provided in medical journal articles.

A fourth main goal of register reporting is to better inform trial participants, patients, and healthcare professionals about trial results (Table 6.2) (International Alliance of Patients' Organisations, 2013; Chan *et al*. 2014; Institute of Medicine, 2015). At least some participants want access to trial results (e.g. to see how they contributed) and many consider this an ethical imperative (Fernandez *et al*. 2003), although there is disagreement (e.g. over what should be shared and how) (*see* Miller *et al*. 2008 for a discussion; Bredenoord *et al*. 2015). For example, as the European Public Health Alliance (EPHA), a public health NGO with 92 member organisations based in 21 countries, strongly argue:

> *"Given that participants in clinical trials act out of solidarity by offering their time and bodies for the benefit of society at large, it is an ethical obligation to make clinical trials results available"* (EPHA, 2013).

There is also evidence that some patients, and especially those with statistical or medical backgrounds, need access to results to inform decision-making (Liberati, 2004; Fischhoff *et al*. 2011; Woloshin and Schwartz, 2013). As Ben Goldacre, a doctor and influential opinion leader, argued when giving evidence to the UK House of Commons Science and Technology Committee (2013):

> *"Healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best"*.

Medical journals can, however; be a poor way of disseminating results to participants, patients and healthcare professionals. One issue is that nonpublication and associated biases means that none of them will be able to access unpublished results. This is especially the case for trials with negative results or that were discontinued (Pica and Bourgeois, 2016). For example, Turner *et al*. (2008) found that among 74 studies examined 34% were not published, which means that for 3,449 participants trial results were inaccessible through medical journals. Participants, patients, and healthcare professionals can also find results difficult to access even when they are published in medical journals. For example, many medical journals are unaffordable because they have expensive subscription fees and pay walls (Van Noorden, 2013). The University of Alberta library recently released data on its annual journal subscriptions, which showed that the University spent over 15 million Canadian dollars on annual journal subscriptions in 2016 with $2,393,657.19 spent on *ScienceDirect* alone (University of Alberta, 2016). Trial participants and patients, in particular, are also unlikely to be equipped to understand medical journal articles especially if they are unfamiliar with them and do not have statistical or medical training. Therefore EMA seeks to use freely and publicly available trial registers to inform participants, patients, and healthcare professionals about results.

(6.3.2) Quantity and quality issues

There has been strong and growing support for reporting trial results in registers over the past two decades (Zarin *et al*. 2015). This has been accompanied by legislative and regulatory changes in Europe and the US (FDA Amendments Act, 2007; EMA, 2014d). Reporting summary levels results has also been discussed as an ethical issue (Zarin and Tse, 2008). Perhaps most notably, the World Medical Association revised the Declaration of Helsinki in 2013 to elevate summary-level results reporting, regardless of whether results are positive or negative, to an ethical obligation:

> *"Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports"* (World Medical Association, 2013).

Concerted efforts have also been made to mitigate under-reporting and associated dissemination biases in medical journals (Wager and Williams, 2013; Brice and Chalmers, 2013; Dal Ré, 2016). In particular, similar to trial registration several influential organisations have strongly encouraged summary-level results reporting (Dal Ré, 2016). For example, while the influential ICMJE stated in 2004 that publishing all clinical trials is an ethical obligation, new journals have been created solely for reporting negative results such as the *Journal of Negative Results in Biomedicine* (*see* Olsen and Pfeffer, 2002). Despite these efforts, however; there are several important issues with EMA's and FDA's trial registers as a mode of dissemination that have significantly limited their effectiveness.

The first significant issue is that, similar to registration, there remains a significant lack of compliance (Prayle *et al*. 2012; Miller *et al*. 2015; Chen *et al*, 2016). Many trialists still do not report the results of clinical trials in registers (Chen *et al*. 2016; Pranic and Marusic, 2016). For example, one recent study (Chen *et al*. 2016) of ClinicalTrials.gov found poor performance and noticeable variation in the dissemination of clinical trial results across leading US academic medical centres, with a range of 16.2–55.3 % of results from clinical trials being disseminated within 24 months of study completion. There has also been variation in register results reporting rates. For example, while vaccine trials have been found to have the highest levels of results reporting (albeit with some time lag) (Manzoli, 2014), non-industry sponsored trials have been found to have very low reporting rates (Chen *et al*. 2016). This is despite EMA and

FDA regulators making it mandatory to publish summary level results in trial registers (Zarin *et al*. 2011; Law *et al*. 2011; EMA, 2014d).

These quantity and nonpublication issues have *a priori* reduced the effectiveness of trial registers in achieving its main goals (Table 6.2). First, publishing all trial results on registers and hence minimising associated biases requires that all summary level results are reported. Second, providing medical researchers with a standardised and structured format of trials will be much less effective if so many trials are not reported in registers. Third, participants, patients, and healthcare professionals wishing to view summary level results and free of charge will not be able to do so if trials are not reported in registers.

Several reasons have been identified for the lack of trial register reporting (i.e. non-compliance). Some have argued that many institutions may be unaware of mandatory reporting requirements (Law *et al*. 2011) or why reporting is important (Smyth *et al*. 2011). Trialists may also have difficulty conducting the necessary data analyses in the time frame given by the regulators (Law *et al*. 2011). For example, some studies have shown that industry is much more likely to report summary level results in both EMA's (Deane and Rawal, 2016) and FDA's (Law *et al*. 2011) registers, which may reflect additional resources and incentives for doing so. There are also arguments that trialists may be concerned about jeopardising their chances of publishing in medical journals (Law *et al*. 2011). For example, journal editors have historically required that, in order to be considered for publication, trial results are not published *anywhere* else. Going further, a systematic review (Scherer *et al*. 2015) found that the main reasons why authors did not publish summary level results was due to an array of factors that trial registers would not necessarily be able to solve. This includes a lack of time, a lack of resources, trouble with co-authors, trialists considering register reporting as a low priority, authors being relocated, or publication not being the aim of the study (ibid, 2015). Therefore there are significant issues with the quantity of trials reported in registers and numerous reasons why trialists may not report results.

An equally significant issue with results reported in registers centres on their quality. In particular, many actors argue that trial registers do not provide the same peer review process as medical journals and hence can be of low quality (Goodman *et al*. 1994; Cobo *et al*. 2007; Science and Technology Committee, 2013; Manzoli *et al*. 2014; Hopewell *et al*. 2014;). This

is important because peer-review is crucial to "the reputation and reliability of scientific research", and can provide quality control, post-publication commentary, and the possibility for correcting errors or retracting studies (Science and Technology Committee, 2011, 2013: 36-37). Indeed, there is clear evidence that many register entries are incomplete or poorly reported (Manzoli *et al*. 2014: 5; Bourgeois *et al*. 2010). Medical journals also have other benefits that are not possible with register reporting including thorough ethical review procedures (De Silva and Vance, 2017). Going further, several actors have long argued that participants and patients may not be able to understand the complicated clinical trial information reported in registers or will have a difficult time assessing the quality of multiple analyses in context (Wager, 2006; Zarin and Tse, 2008). For example, recent studies have made clear that even the proposed 'layperson' summary documents, regardless of the original trial entries originally intended for medical researchers, may be difficult to understand (e.g. without understanding the clinical trial process) (Sroka-Saidi *et al*. 2015; Chamberlain-James, 2015; Nottbohm *et al*. 2016).

These data quality issues have led many actors to argue that, although posting in registers can help to limit issues of reporting biases (Riveros *et al*. 2013), publishing in medical journals still needs to be done (Manzoli *et al*. 2014). The UK House of Commons Science and Technology Committee (2013: 1) "favoured publication of summary level data in peer-reviewed journals" as the best mode of results dissemination. The UK Academy of Medical Sciences and the Cochrane Collaboration's meta-analysis methods group also recommend the use of medical journals as the most appropriate and most preferable mode of summary level results transparency (Science and Technology Committee, 2013). Director of ClinicalTrials.gov Deborah Zarin made clear that FDA' register is intended to "complement not replace" medical journal publication (Zarin *et al*. 2011). Therefore reporting summary levels results in trial registers such as EU-CTR is not considered the 'holy grail' of results reporting and important information quality issues need to be addressed beyond ensuring that all trials are reported. Taken together, these two factors, the quantity and quality of transparency, has significantly impacted the effectiveness of trial register reporting.

(6.4) Clinical study reports

The third level of clinical trial transparency is clinical study reports (CSRs) (level 3). CSRs are documents written by pharmaceutical companies and used by EMA for licensing approvals and other scientific evaluations such as post-authorisation safety studies. They provide much more granulated and detailed information on a clinical trial than can be found in the published literature. They also differ from trial registration and summary results transparency because CSRs *must* be submitted to the regulators in order for a medicine to be approved (Science and Technology Committee, 2013) As Doshi *et al*. (2012) concisely put it:

> *"When regulators decide whether to register a new drug in a manufacturer's application, they review the trial's clinical study report".*

This means that, compared to trial registration and summary-level results reporting, the regulators have complete control over the quantity of CSRs made public. Although CSRs do not provide as much detail as participant-level data (Koenig *et al*. 2014), they can still amount to hundreds, if not thousands, of pages on a clinical trial, which includes overviews, summaries, appendices, protocols and protocol amendments, sample case reports, forms, and documentation of statistical methods. For example, Doshi and Jefferson (2013b) reported that a total of 144,610 pages of scientific and medical affairs data and information was contained in a sample of 78 CSRs, or a mean average of just over 1,850 pages each.

CSRs submitted to EMA have historically not been accessible to those outside the regulatory network (including the pharmaceutical company that created them). Since December 2010, EMA as provided access to CSRs through its reactive access to documents policy (i.e. written requests for documents) (Chapter V). On 2nd October 2014, and after much debate, EMA announced a new proactive transparency policy on CSRs (EMA, 2014a, 2014b). While the agency continued to provide access through written requests, the new policy meant that most CSRs, submitted under the centrally authorised procedure after January 1st 2015, would be published on an online web-portal (clinicaldata.ema.europa.eu) (i.e. proactive transparency). The policy excluded CSRs submitted before January 2015 and information considered confidential. It also did not apply to non-centrally authorised medicines.

On 20th October 2016, EMA uploaded CSRs for two newly approved medicines under its new policy. This resulted in the online publication of approximately 260,000 pages of data and information for over 100 CSRs relating to (1) a medicine used to treat multiple myeloma (a cancer of the bone marrow) called Kyprolis (carfilzomib), and (2) a medicine used in adults with gout to reduce high levels of uric acid in the blood called Zurampic (lesinurad) (EMA, 2016). This made EMA the first and, up until at least the end of the case study period (December 2016), the only authority in the world to provide public online access to CSRs (Hunter, 2015). As EMA's 3rd Executive Director, Guido Rasi (2016) stated:

> *"We have a pioneering approach to transparency. We are the first regulator in the world to allow researchers and academics, and the public as a whole, access to the clinical data on which marketing authorisations are based".*

(6.4.1) Goals and audiences for level 3

In contrast to the first two levels of clinical trial data transparency, the proactive publication of CSRs has received the lion's share of attention from a multiplicity of actors (Chapter V). This attention has included strong demands that EMA publishes all CSRs immediately (e.g. arguments that full disclosure is an ethical obligation), substantial criticisms of EMA's policy itself (e.g. arguments that full disclosure will have serious negative and irreversible consequences), and significant external pressure on the regulators from all actors (Chapter V) (Bouder *et al*. 2015; Way *et al*. 2016). Indeed, one of the main reasons why EMA's CSRs policy has received so much attention, especially when compared to registration and trial register results reporting, is that EMA has substantial control over the transparency of CSRs.

The overriding goal of EMA's 2014 CSRs policy is to enable outsiders to freely re-analyse the data and information that underpins decision-making in EMA's scientific committees (Table 6.3). In turn, this is expected to achieve at least six secondary goals for different actors. This includes goals for external medical researchers (e.g. University Academics) and health technology assessors (e.g. assessors at the UK National Institute for Health and Care Excellence [NICE]), industry and clinical trialists, as well as patients (i.e. medicine-users), the public, and healthcare professionals (e.g. doctors, pharmacists, and nurses). These goals and their connected audiences are addressed in turn.

Table 6.3: Seven goals and connected audiences of EMA's 2014 CSRs policy

Overriding goal	Secondary goals	Target Audiences
Enable secondary re-analysis of input data	Improve the scientific knowledge base on pharmaceuticals	Medical researchers
	Overcome the failure of registration and results reporting to mitigate reporting biases	Medical researchers
	Scrutinise regulatory decisions	Medical researchers
	Enable fully-informed decision-making for non-EMA decision-makers	Health technology assessors
	Improve the efficiency and effectiveness of drug development and the clinical trial process	Industry and clinical trialists
	Better inform patients, the public, and doctors about the benefits and risks of medicines	Patients, the public and medical doctors

The first goal of enabling secondary re-analysis of CSRs is to improve the scientific knowledge base on pharmaceuticals (Table 6.3) (Bonini *et al*. 2014; Eichler *et al*. 2013). Considering companies are legally required to submit all scientific data to EMA when seeking regulatory approval, medical researchers, in particular, can gain a full picture of the safety and efficacy of every medicine authorised by the agency. High quality scientific (re)analyses of CSRs can provide opportunities for exploratory research that may lead to "new hypotheses about the mechanisms of diseases, more effective therapies, or alternative uses of existing abandoned therapies" (Institute of Medicine, 2015: 28). CSRs can also be combined with other datasets, or analyses could be made that industry and other "traditional institutions would not normally conduct" (e.g. analyses that may not be their priority) (Eichler *et al*. 2012). As four senior EMA regulators explained in the *New England Journal of Medicine*:

> *The EMA encourages reanalysis of data to expand our body of knowledge and improve drug research. Data recipients should be granted complete freedom to engage in exploratory re-analyses aimed, for example, at optimising future study designs with regard to population selection and sample size, choice of outcomes, definitions of*

> *clinically relevant differences for various end points, or identification of biomarkers for better disease phenotyping* (Bonini *et al*. 2014).

If successful this can provide patients with safer and more extensively and intensively investigated medicines. Independent expert re-analyses can also support the regulators by providing added expert capacity and hence aid scientific committees in decision-making (Feys, 2013). As EMA regulators stated in 2016:

> *"[EMA's CSRs policy will] facilitate the independent re-analysis of data by academics and researchers after a medicine has been approved. This will increase scientific knowledge, and potentially further inform regulatory decision making in the future"* (EMA, 2016a).

Outsiders, especially external medical researchers who publicly demanded EMA enhance transparency (e.g. Doshi *et al*. 2012) (Chapter V), are therefore expected to conduct rigorous scientific studies by (re)using publicly available data and information published online.

The second goal of enabling secondary re-analysis of CSRs is to overcome some of the issues of nonpublication and associated biases that haven't been achieved through reporting results in medical journals or trial registers (Section 6.2). This argument has been put forward predominately by systematic reviewers and data-miners (e.g. Gøtzsche, 2011). For example, in seeking to re-analyse all evidence on neuraminidase inhibitors (a class of drugs that are commonly used as influenza antivirals), several Cochrane Collaboration researchers stated:

> *"We have become convinced that the answer [to conducting complete systematic analyses] lies in analysing clinical study reports rather than the traditional trials appearing in biomedical journals"* (Doshi *et al*. 2012)

By overcoming issues of nonpublication and associated biases, these actors argue that many of the goals already discussed can be achieved (Walport and Brest, 2011; Jefferson *et al*. 2011; Doshi *et al*. 2013, 2013b; Chalmers *et al*. 2014; Institute of Medicine, 2015). This includes reducing scientific resources wastage, reducing unnecessary harm to participants, and facilitating systematic reviews and other analyses of the literature (*see* section 6.2).

One argument is that medical researchers can obtain all 'invisible' trial results because they have to be reported in CSRs in order for a medicine to be approved (Wieseler *et al*. 2012; Doshi

et al. 2013; Doshi and Jefferson, 2013b; Maund *et al*. 2014). For example, Wieseler *et al*. (2013) compared the published literature – including medical journals and trial registers – with 101 CSRs received by the German health technology agency, the Institute for Quality and Efficiency in Healthcare (IQWiG). The study found that, in sharp contrast to CSRs, publicly available sources provided insufficient information on patient-relevant outcomes (Wieseler *et al*. 2013). This means that publishing CSRs could potentially minimise publication bias (Science and Technology Committee, 2013). For example, medical researchers could identify what trials have been published or not and, in turn, update/conduct systematic analyses that include both negative and positive results (Doshi *et al*. 2013).

A second argument is that outcome reporting bias can be minimised with full CSRs transparency (Vedula *et al*. 2013; Maund *et al*. 2014; Hodkinson *et al*. 2016). CSRs provide information on all trial outcomes, whether they are positive or negative, as well as full protocol information and amendments (EMA, 2014b). External researchers could use this information to see what outcomes were reported in the published literature and compare these to the original protocols reported in CSRs (Vedula *et al*. 2013). For example, Maund *et al*. (2014) analysed CSRs with 13,729 pages that were obtained from EMA in May 2011 on request (i.e. through its reactive policy). The authors found inconsistencies between protocols and outcomes in one trial that would not have been identified otherwise (Maund *et al*. 2014). Therefore two of the most significant reporting biases could therefore arguably be minimised with EMA's CSRs policy.

The third goal of enabling secondary re-analyses of CSRs is to enable medical researchers and other interested outsiders to scrutinise industry data and regulatory decisions (Goldacre, 2012; Doshi *et al*. 2013; Chan *et al*. 2014). This goal has been underpinned by strong criticisms of pharmaceutical companies and the regulators themselves with some claiming that the system is "broken" and needs "fixing" (e.g. Goldacre, 2012). These criticisms have been accompanied by numerous books, commentaries, and public attacks on industry and the regulators (Abraham and Lewis 1999, 2000; Angell, 2004; Smith, 2005; Garattini, 2005; Garattini and Bertele, 2007; Goldacre, 2012; LaMattina, 2013), as well as an influential activist group (AllTrials.com, 2014). As Tom McKillop, ex-Astra Zeneca chief executive officer, commented several years earlier:

> "*Our reputation has never been as low. We are now rated broadly in line with the tobacco industry. [...] The industry's reputation is so low that it makes it very difficult for us to argue our case with politicians and society in general*" (Löfstedt, 2007: 471).

Along with other criticisms (e.g. industry spending too much money on marketing rather than research and development), the sector has been plagued by high profile drug withdrawals (e.g. Baycol and Vioxx) and post-marketing safety concerns (e.g. Avandia and Zelnorm) (Angell, 2004; Avorn, 2004; Löfstedt, 2007; Eichler *et al*., 2008; Goldacre, 2012), as well as other safety-related incidents (e.g. Mediator and Poly Implant Prothèse breast implants) (Mullard, 2011; Looney, 2012). Industry has also been accused of deliberately concealing data (Goldacre, 2012). For example, in 2014 two pharmaceutics companies, Takeda and Eli Lilly, received record fines of a total of 9 billion US dollars for "hiding evidence suggesting that their Actos diabetes medicine might expose patients to a heightened risk of bladder cancer" (Jack, 2014). Although there has been heated debate, one main argument is that the regulators are no longer trusted to analyse CSRs in private (Laine *et al*. 2007; Löfstedt and Way, 2016a; Bouder *et al*., 2015). As EMA Executive Director, Guido Rasi, commented:

> *"Some scandals increase distrust, and that's why we have to rebuild the trust and say, 'OK, you want to see the data that I see to make my decision? Here are the data.' Why not?*" (Khamsi, 2012).

Therefore EMA's CSRs policy seeks to enable 'independent' expert re-analyses of CSRs in order to hold the regulators and industry accountable, identify conflicts of interest (e.g. in the regulators' interpretation of clinical trial data) and, in turn, create a more robust pharmaceutical system.

A fourth goal of enabling secondary re-analysis of CSRs is to provide additional information to Health Technology Assessors (HTAs) and hence enable fully informed decision-making (McGauran *et al*. 2010; Wieseler *et al*. 2012; IQWiG, 2013; NICE, 2013). HTAs weigh up the benefits and risks of medicines and undertake "a multidisciplinary process that summarises information about the medical, social, economic, and ethical issues related to the use of a health technology" (EUnetHTA[47], 2017). Although CSRs are accessible to the EU regulatory network[48], HTA (and regulators operating outside the EEA) often have to rely on assessments

[47] European Network for Health Technology Assessment
[48] This includes the EU Commission, NCAs, and EMA, as well as the pharmaceutical companies that wrote them.

made by EMA through its centralised procedure. Several HTAs have argued that their agencies need full CSRs for fully informed decision-making (McGauran *et al*. 2010; Wieseler *et al*. 2012). As the German agency, IQWiG, argues:

> *"Full trial information and results are needed for HTA agencies to be able to provide appropriate and meaningful assessments of drugs and other health technologies within their remit"* (IQWiG, 2013: 51).

Many of these arguments centre on the failure of nonpublication and associated biases in the medical literature (section 6.2) (IQWiG, 2013). For example, in comments submitted to EMA, the EUnetHTA[49] commented that HTAs need CSRs because "[scientific journals] are insufficient to provide a complete and unbiased picture of a drug" (EUnetHTA, 2013: 51; IQWiG, 2013). Therefore several prominent HTA bodies have argued that, if CSRs are not available their decision-making will be unreliable and not based on the best available evidence. In turn, EMA's CSRs policy is expected to decrease expenditure on ineffective interventions or interventions that are less effective than others (EUnetHTA, 2013: 51; IQWiG, 2013). As the UK agency NICE (2013: 67) argues, if CSRs are not made available, cost effectiveness decisions may "be made on unreliable valuations that could lead to negative consequences for patients and the efficiency of healthcare systems".

A fifth goal of enabling re-analyses is to improve the efficiency and effectiveness of drug development and the clinical trial process (Eichler *et al*. 2013; Institute of Medicine, 2015). These arguments were most prominently made by senior EMA regulators when stating:

> *"It is ironic that the organizations that most resist wider access to data are the ones that stand to benefit so much from greater transparency"* (Eichler *et al*. 2013).

For industry, the regulators argue that CSRs transparency may result in improvements in the design and analysis of subsequent trials, speed up the development of drugs (e.g. streamline development), enhance a drug's value in the marketplace (e.g. improve comparativeness effectiveness analysis), and reduce duplication effort amongst trial sponsors by, for example, preventing "repositions of trials that are doomed from the outset" (*see* Eichler *et al*. 2013 for a discussion). For improving the clinical trial process more generally, many further arguments

[49] This is a joint opinion from 33 organisations from across Europe.

have been provided (Institute of Medicine, 2015). These include trialists taking more care with recording results (e.g. because they know that outsiders may review their work), and CSRs informing future research designs (e.g. trialists building on previous work) (Bonini *et al*. 2014; Chan *et al*. 2014; Institute of Medicine, 2015: 32). In turn, the pace of scientific discovery is expected to greatly improve partly because the whole research enterprise will be more efficient and effective (Walport and Brest, 2011). EMA's CSRs transparency policies therefore seek to benefit industry and improve the efficiency and effectiveness of the clinical trial process.

A six goal of enabling re-analyses is to better inform patients, the public, and healthcare professionals about the benefits and risks of medicines Adams, 2015; Chan *et al*. 2014). As Cohen and Billingsley (2011) argue: "[data sharing is expected] to help clinicians and patients make better informed decisions". Although this objective has received far less critical examination, EMA made clear when launching its 2014 CSRs policy:

> *"EMA expects the new policy to increase trust in its regulatory work as it will allow the general public to better understand the agency's decision-making."* (EMA, 2014a).

Or, as the agency stated after first proactively releasing CSRs with 260,000 pages for two newly authorised medicines, Kyprolis and Zurampic:

> *"With EMA's proactive approach to providing access to the data, patients and healthcare professionals will be able to find out more information about the data underpinning the approval of medicines they are taking or prescribing"* (EMA, 2016a).

Therefore one main argument is that patients and healthcare professionals "need access to help make informed decisions" and to gain a 'complete picture' of the relative benefit-risks of medicines (Rodwin and Abramson, 2012: 872). This means that EMA's transparency policies seek to provide patients and prescribers with empowering medicines information and data (EMA, 2014a, 2014b, 2016a; Adams, 2015). The expectation is that EMA will be viewed as 'transparent' as it will not be 'hiding' or 'concealing' any information from the public (personal communication, 2014). Patients are also expected to have a better understanding of how EMA's committees need to balance difficult decisions when approving medicines or as the Institute of Medicine makes clear:

> "*Patients and the public will have a better understanding that numerous judgements are needed to transform source data"* (Institute of Medicine, 2015: 32).

In turn, all of these goals are expected to build public trust in the regulators and EMA's centralised medicines authorization system (although the connection between EMA's policies and trust is rarely discussed in detail) (Adams, 2015; O'Reilly, 2015; EMA, 2015a).

(6.4.2) Confidentiality and data privacy

Without doubt the single most controversial and widely discussed issue over EMA's publication of CSRs policy has centred on commercially confidential information (Gøtzsche and Jørgensen, 2011; Ombudsman, 2010; Roche, 2012; EMA, 2013e, 2014b; Pfizer, 2013; EFPIA and PHrMA, 2014; Hunter, 2015). Similar to other EU bodies and institutions, EMA is obliged to protect commercial confidentiality under European law (e.g. Regulation (EC) No 1049/2001/EC). Yet, there have been many arguments that EMA's CSRs policy does not go far enough in doing so. For example, Peter Bogaert, managing partner at law firm Covington & Burling, bluntly stated:

> *"It is obvious that providing full access to all data that were submitted with a marketing authorisation application, to the public at large, including actual or potential competitors, can undermine the commercial interests of the pharmaceutical company involved"* (Hunter, 2015).

One argument is that pharmaceutical innovation and competitiveness will be risked if company trade secrets are shared when making CSRs public (Eichler *et al*. 2013; Norgine, 2013; Pfizer, 2013; BioIndustry Association, 2013; PhRMA and EFPIA, 2013). Competitors could 'free-ride' off investments by accessing CSRs (and hence proprietary information) (PhRMA and EFPIA, 2013). This could weaken incentives for companies to invest in pharmaceutical research, create unfair competition (e.g. competitors shortening their medical product development plans) (BioIndustry Association, 2013; IFAH-Europe[50], 2013; Romanian ARPIM[51], 2013; PhRMA and EFPIA, 2013), or, as the pharmaceutical company Norgine (2013) argues:

[50] International Federation for Animal Health Europe
[51] Romanian Association of International Medicines Manufacturers

> *"...competing pharmaceutical companies could engage in re-analysis of each other's data leading to vexatious challenges to the regulatory process".*

A second argument is that companies from other regulatory jurisdictions could use CSRs made public in the EU (Lang, 2013). Companies operating outside the EU cannot be easily monitored or policed as they are beyond EMA's jurisdiction (IFAH-Europe, 2013). One concern is that making CSRs public may therefore impact negatively on companies as countries have "different standards of regulatory data protection, and may prejudice intellectual property rights" (Pfizer, 2013: 85). For example, competitors may use CSRs for competing products in countries that do not recognize data exclusivity or have weaker patent rules (e.g. India or China) (Kapczynski, 2014; Chowdhury *et al*. 2016).

However, EMA regulators argue that issues around commercial confidentiality has been exaggerated and that industry have been overly defensive over sharing CSR data (Eichler *et al*. 2013). In particular, senior EMA regulators argue that their policy will foster industry innovation (also *see* section 6.4.1):

> *"Contrary to industry fears, we argue that access to full – though appropriately deidentified – data sets from clinical trials will benefit the research-based biopharmaceutical industry. We predict that it will help to increase the efficiency of drug development, improve cost-effectiveness, improve comparative-effectiveness analysis, and reduce duplication of effort among trial sponsors"* (Eichler *et al*. 2013).

With that said, commercial confidentiality issues have been a persistent and significant resource-intensive issue for EMA (personal communication, 2015). Beyond being pressurised by industry, the agency has been sued numerous times over providing access to CSRs through its reactive policy (EMA, 2013e; EMA, 2017j).

Two examples have been particularly challenging for EMA. First, in 2013 two pharmaceutical companies, AbbVie and InterMune, sought and obtained injunctions against EMA to stop the agency from releasing CSRs and other detailed information on two drugs: Humira (adalimumab) for rheumatoid arthritis and Esbriet (pirfenindone) for idiopathic pulmonary fibrosis (EMA, 2013e). As an interim decision, EMA was ordered by the General Court of the EU not to provide the requested documents until a final ruling was given (EMA, 2013e). Although the case was eventually settled outside of court, EMA did not get legal clarity over commercial confidential information contained in CSRs (personal communication, 2014).

Second, in December 2015 two court cases were brought to EMA by PTC therapeutics and Intervet over public requests for access to CSRs relating to Translarna (ataluren) for Duchenne muscular dystrophy and three toxicity studies for Bravecto (fluralaner) a veterinary medicine used to treat flea infestations in dogs and cats (EMA, 201j). Again the General Court of the EU ordered EMA not to provide the requested documents until the final ruling was given[52] (EMA, 2017j). These cases highlight that there are significant legal challenges with making CSRs publicly available and at the very least that CSRs transparency has substantially increased legal action against the agency.

Along with commercially confidential information issues, data protection and patient privacy concerns relating to EMA's CSRs policy have been much debated (GlaxoSmithKline, 2013; Pfizer, 2013; Roche, 2013; EMA, 2014b; Koenig *et al*. 2014). One main concern is that publishing CSRs will weaken safeguards for clinical trial participants. Providing full public access to CSRs presents a risk because they can contain identifiable information about clinical trial participants (Institute of Medicine, 2015) and, as ECCO[53] (2013) argues, "avoiding the retrospective identification of individuals is fundamental". For example, CSRs can contain participant information relating to genetic data, stigmatised diseases (e.g. HIV/AIDS), communicable diseases, drug injections, and mental health issues, which could result in abuse, harm or other unwanted consequences (Gymrek *et al*. 2013; MRCT[54], 2013; GCGMA[55], 2013; Institute of Medicine, 2015). In addition, volunteers may be unwilling to participate in clinical trial research due to concerns that data will be given to third parties and the public (Koenig *et al*. 2014).

A second closely connected issue centres on medical personnel such as trialists being identified (EHA[56], 2013: 72; GlaxoSmithKline, 2013; IFAH-Europe, 2013). In particular, there is a risk that individuals will be identified in CSRs and singled out by activists, patients, survivors, and others (EHA, 2013). For example, there have been many issues with pharmaceutical company and research institution employees being identified by animal rights activists (IFAH-Europe, 2013; Reardon, 2017). As one pharmaceutical company commented:

[52] The cases were still on-going at the time of writing (EMA, 2017).
[53] European Crohn's and Colitis Organisation
[54] Multi-Regional Clinical Trials Center at Harvard University
[55] Drug Commission of the German Medical Association
[56] European Haematology Association

> *"The inclusion of company personnel names poses significant risks for individuals. A number of [GlaxoSmithKline] employees have been targeted by animal rights extremists, even though they have not been directly involved in animal research"* (GlaxoSmithKline, 2013: 57).

In responding to these concerns, EMA's policy commits to anonymising individual information (EMA, 2014b, 2017k). There are, however, difficult challenges with anonymising data and deidentifying individuals. First, on the most basic level, anonymisation will mean that some data will not be made available and cannot be re-analysed (EFSPI[57], 2013: 10; PhUSE[58], 2013). This exemplifies why full disclosure may not be desirable or feasible. Second, anonymisation is immensely complicated with some arguing that it is impossible to completely deidentify individuals (EFSPI, 2013: 99). One of the main areas of concern has been with orphan drugs (i.e. drugs that treat rare diseases). For example, patients with rare diseases can be more easily identified in CSRs as there are fewer individuals with the diseases and smaller sample sizes reported (IAPO, 2013). For example, the pharmaceutical company Pfizer, (2013: 95) comment:

> *"A constellation of seemingly general information may only too easily lead to identify of individuals within these small patient populations who may already be stigmatized and vulnerable"* (Pfizer, 2013: 95).

A second issue is that EMA has had to commit substantial resources to CSRs anonymisation. For example, in March 2017 EMA announced a call for experts to join a new technical anonymisation group to help the agency develop best practices:

> *"Anonymisation of clinical reports poses a major challenge to those directly involved (pharmaceutical industry, clinical research organisations and EMA) and to those accessing the data (patients, healthcare professionals and academia). [...]. As data anonymisation is a rapidly evolving field, EMA wants to keep abreast of developments and continue to update the guidance with the support of experts."* (EMA, 2017k).

Third, several patient representative groups argue that EMA's policy does not go far enough to protect retrospectively identified patients (EORTC[59], 2013, IAPA[60], 2013). For example, EORTC (2013) comments: "Who would be responsible or liable if a patient's identity was divulged due to inappropriate handling of data?" This issue is complicated by that fact that

[57] The European Federation of Statisticians in the Pharmaceutical Industry
[58] The Pharmaceutical Users Software Exchange
[59] The European Organisation for Research and Treatment of Cancer
[60] The International Alliance of Patients' Organisations

once CSRs are made public they cannot be returned, or, as IAPA (2013: 95) put it, attempting to rectify any data protection breaches after CSRs have been published is "tantamount to closing the barn door once the horse escapes". There are therefore many challenging issues with anonymising CSRs and not least substantial EMA resource consumption.

(6.4.3) Poor quality re-analyses

Although *high quality* re-analyses of data are expected to achieve many of EMA's re-analysis goals, *poor quality* analyses of data could equally have detrimental outcomes and reverse effects for patients and public health (Way *et al*. 2016). These issues have been discussed at great length in the medical community including in a notable 2015 Institute of Medicine report (*see* Institute of Medicine, 2015 for a full discussion). Some of the most widely discussed include the potential of distorting the scientific basis for decision-making by, unintentionally or otherwise, coming to incorrect conclusions, reducing the efficiency of medical investigations (e.g. by creating disincentives for trial sponsors), creating adverse effects for patients (e.g. discouraging patients to take certain safe and effective medicines), and producing unnecessary anxiety for patients receiving inaccurate or publicly contested information (Eichler *et al*., 2012a; Spertus, 2012; Mello *et al*., 2013; EORTC, 2014; IAPO, 2013; Institute of Medicine, 2015: 29). As Will Greenacre (2014), policy officer at the Wellcome Trust, and others[61] jointly commented:

> *"Potential harm could result from wrongful secondary interpretation of clinical trial data. Whilst we agree that greater openness could put clinical trial data under productive scrutiny, the consequences of secondary analyses that wrongfully contradict the published findings could be severe, and are certainly not in the interest of public health."* (Greenacre, 2014).

One widely discussed concern, for example, is that outsiders could misinterpret the complicated medicines information posted online (e.g. relating to adverse reactions or pharmacological effects), that can take over a year for trained reviewers to analyse, leading to a loss of public confidence in a medicine that can significantly affect a patient's well-being. Although there are many other arguments, the overall expectation is that EMAs policies will,

[61] Joint comments submitted to EMA from the Academy of Medical Sciences, Association of Medical Research Charities, Cancer Research UK, the Medical Research Council, Parkinson's UK, and the Wellcome Trust.

optimistically, result in higher rather than poorer quality scientific analyses by outsiders that will lead to beneficial and desirable outcomes for public health.

(6.4.4) Capacity of outsiders to re-analyse

Beyond poor quality analyses, a second issue is whether there is sufficient interest by medical researchers to re-analyse data. In particular, beyond the Cochrane Collaboration requesting data from EMA, how many medical researchers actually want access to CSRs and have the capacity to re-analyse them? At the time of writing, there was no available data on which audiences of EMA's policies have actually been accessing (or not) CSRs on EMA's web-portal (clinicaldata.ema.europa.eu). Indeed, few CSRs were released *proactively* during the case study period. However, illuminating data were available on EMA's reactive access to document policy between 2010 and 2013 including how many requests were made and which transparency audiences made those requests (Figure 6.2) (Bonini *et al*. 2014). The data shows that between 2010 and 2013 pharmaceutical companies (33.5%), law firms (17.5%) and the lay media (15.9%) were the three highest requestors of documents held by the agency, while academic or research institutions received the greatest number of pages (646,207). In contrast, only 5.5% of requests came from the 'general public' *per se* and 3.7% from Health Care Professionals.

These findings were much discussed at policy meetings attended by the investigator during the case study period (Chapter IV). Indeed, although the data concerns EMA's 2010 reactive transparency policies (EMA, 2010a), it does have several implications for EMA's 2014 CSRs policy and its effectiveness. One of the most significant issues is that far fewer medical researchers requested access to documents than EMA regulators expected or were hoping (personal communication, 2014). This means that EMA's policy is highly likely to be less effective in achieving its goals for medical researchers. One main reason why so few EMA documents were requested from medical researchers is that few researchers outside of regulatory agencies are even aware of their existence, or as Doshi *et al*. (2013) put it: "Outside of regulatory agencies, few researchers have ever heard of clinical study reports". This means that researchers outside the regulatory network, who are expected to re-analyse data, are likely to be inexperienced in mining CSRs. Although researchers may become more aware of CSRs and more sophisticated in analysing such large datasets over time, this still presents a

significant issue affecting the effectiveness of EMA's proactive policy. How will external researchers re-analyse CSRs if they are unfamiliar with them and unaware of their existence?

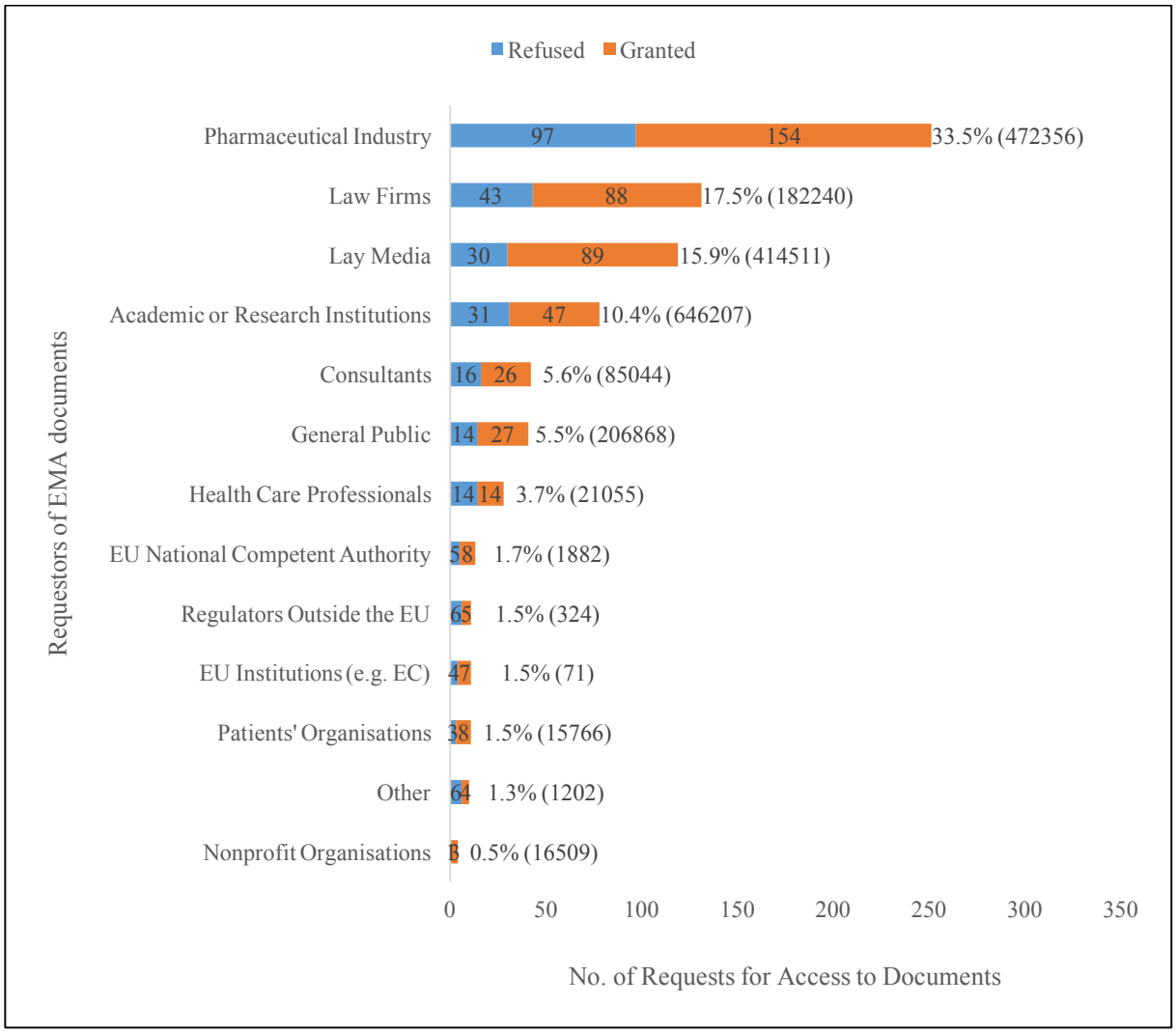

Figure 6.2: Bar chart showing the number of requests and distribution of requestors for access to EMA documents that were either refused (blue shading) or granted (orange shading) between 2010-2013. Parentheses show the number of documents released for each requestor. EC denotes European Commission. EU denotes European Union. Source data: Bonini *et al*. (2014).

(6.4.5) The role of intermediaries after re-analysis

EMA's goal of providing patients and doctors with a better understanding of the benefits and risks of medicines is also poorly understood. One assumption with CSRs policies is that more information will lead to a better understanding in a simple one-way model of communication. Patients and doctors could potentially obtain such an understanding *directly* by going online

and reading CSRs for themselves (clinicaldata.ema.europa.eu). In turn, they can potentially gain a better understanding of medicines they use or may use (EMA, 2014b: 5). Indeed, EMA's web-portal is free to use and available to anyone with access to the Internet. However, this is rather unlikely. As Thomas Lang, Austrian Medicines & Medical Devices Agency (AGES), argues:

> *"The benefit to the EU population and patients will not be direct, but indirect only. Individual patients will not have the capacity to process data and set these into the context of a complex decision making system. This is only feasible through the responsible work by third party experts. Therefore, the true benefit will be that further, hopefully independent, opinions become available to the public."* (Lang, 2014).

This means that patients and doctors are more likely to *indirectly* receive information on CSRs through intermediaries (e.g. the news media, doctors, external researchers, medical journals, non-governmental organizations and others). Intermediaries are therefore essential to the effectiveness of EMA's transparency policies for both (1) enabling re-analyses and (2) better informing patients, the public, and doctors about the benefits and risks of medicines.

Patients and doctors can be expected to receive new information on benefits and risks indirectly in two main stages. In the first stage, those 'outside' the traditional regulatory network – and especially 'independent' medical researchers (e.g. Cochrane collaboration researchers) – are expected, and encouraged, to re-analyse CSRs uploaded onto EMA's web-portal. In the second stage, these outsiders are expected to convey the findings of re-analyses to patients and doctors in two possible ways. The first way is that outsiders might convey the results of re-analyses to EMA directly and exclusively. This may (or may not) result in the agency communicating new information about the benefits and/or risks of a medicine to patients and doctors such as by using well-established agency risk communication tools (e.g. updating packaging information or recalling a medicine now deemed unsafe) (*see* Way *et al*. 2017). For example, this might include sharing information with the public, changing beliefs, or changing behaviour and can be considered as an output transparency mechanism as the results will have been reviewed by EMA's scientific committees (Way *et al*. 2017).

The second, and much more likely, way is that outsiders will convey results to patients and doctors themselves without (first) contacting the EMA but instead through various other information channels (e.g. the media, medical journals, patient group representatives, the

Internet etc.) (Maund *et al*. 2014; Ebrahim *et al*. 2014; Jefferson *et al*. 2016). This is the most likely way that the results of re-analyses will be conveyed to patients and doctors. Moreover, whether re-analyses are conveyed to the regulators first or not, many patients and doctors are expected to receive (Bonini *et al*. 2014), and have already received (e.g. Butler, 2014), new information about the benefits and risks of their medicines through secondary re-analyses of CSRs[62].

There is clear evidence that this second route is the most likely way that patients and doctors will receive more information through EMA's CSRs transparency policy, although this does not necessarily mean they will gain a better understanding. First, the usual route of conducting systematic analyses and re-analyses of data has been to go through other routes, rather than to contact the regulators first. For example, after the Cochrane collaboration conducted a systematic review of the literature the organisation published the results on its website, submitted a paper to a medical journal and announced its findings through its own information channels (e.g. the news media). Second, there is evidence from what medical researchers have done with CSRs requested from EMA's (i.e. its reactive policy) and from other sources (e.g. courts demanding companies release data or FOI requests) (Maund *et al*. 2014). For example, this has happened in several cases relating to de-worming treatments, antidepressants etc. Furthermore, Ebrahim *et al*. (2014) conducted a review of re-analyses and found that positive confirmatory re-analyses were less likely to be conducted than negative re-analyses that question the regulators interpretation.

Third, there are real examples that can be taken from the Tamiflu saga (Löfstedt and Way, 2016b). After receiving CSRs the Cochrane collaboration announced its results, which subsequently received global new coverage [first]. There is clear evidence that this is one of the main routes (Gøtzsche and Jørgensen, 2011; Loder *et al*., 2014). After receiving documents held by EMA, the Cochrane Collaboration, an external network of researchers and collaborators (Cochrane, 2014), published an online review of Tamiflu (oseltamivir) (Jefferson *et al*., 2014a), which was subsequently reported in several medical journals (e.g. Jefferson *et al*., 2014b) and, in turn, various news outlets across Europe including *The Guardian*, *Financial Times*, *Daily Mail*, *Der Spiegel,* and *Le Monde* (Boseley, 2014b; Ward and Neville, 2014; Der

[62] They are, however, unlikely to be aware that the information they received came from a re-analyses of EMA's CSRs.

Spiegel, 2014). The open-access report, published by the external researchers, demonstrates how information released by EMA under its transparency policies is most likely be conveyed to the public indirectly through information mediators.

However, this does raise important questions over how medical researchers will communicate the findings of their CSRs re-analyses to patients and doctors. Again the Cochrane saga highlights some of these issues. In particular, Cochrane announced that their findings showed the drug was less effective than the pharmaceutical company, Hoffman-La Roche, had claimed and there was "no good evidence to support claims that it reduces admissions to hospital or complications of influenza" (Cochrane, 2014). Since Cochrane released their findings there has been continued debate over Tamiflu and Cochrane's (re)analysis with some raising important questions concerning the accuracy of the researchers' findings and appropriateness of their policy suggestions (Muthuri *et al*., 2014; Kmietowicz, 2014; Public Health England, 2015; Dobson *et al*., 2015). The potential benefits and difficulties of analysing large data sets with highly complicated safety-related information where even a well-established and highly competent organisation such as the Cochrane Collaboration can come to disputed conclusions. It also shows that publishing CSRs online can lead to more public disputes over data with the regulators being less involved and industry being criticized heavily. However, what is needed is more information from the perspectives of patients and doctors, which is where this thesis turns next.

Chapter VII: PATIENT AND DOCTOR SURVEYS

In order to generate more evidence on EMA's input transparency policies, this chapter presents and analyses the results of the patient (N=1,010) and doctor (N=1,005) surveys (Chapter IV)[63]. What is needed is more evidence from the perspectives of patients and doctors in this new environment. This includes the quantity and quality of medicines information patients and doctors currently receive, their knowledge and awareness of the regulators and their risk communication activities, the trustworthiness and usefulness of intermediaries conveying the results of re-analyses, and opinions on whether the results of re-analysed CSRs should be conveyed before or after regulatory approval, as well as the reactions of patients to receiving new information on their medicines from non-regulatory sources. To be clear, although this chapter presents statistical generalisations about patients and doctors, its primary purpose is to generate evidence on the perspectives of patients and doctors to inform the overall evaluation of the effectiveness of EMA's input transparency policies in Chapter VIII (*see* Chapter IV for a detailed explanation).

In the context of this new more open information environment, the two surveys examined the perspectives of patients and doctors in four main ways. First, they examined the state of the medicines information and communication environment (that is, in late 2014 and early 2015). This means that the questions were asked shortly after EMA published its final October 2014 CSRs policy. In particular, respondents were asked questions on the quantity and quality of medicines information that patients and doctors receive. This revealed, for instance, opinions on how well information is currently communicated to these two actors and the influence of politics and the media on information quality.

Second, the surveys examined respondents' perspectives on pharmaceutical regulatory bodies including EMA and (relevant) NCAs. This includes questions on whether they have heard of them (i.e. awareness questions), and how well they understand the regulatory system (i.e. knowledge questions). This was important in order to understand how patients and doctors view the regulators and their contribution to the pharmaceutical evaluation system.

[63] The results of the patient and doctor surveys were also published in two *Journal of Risk Research* papers (Way *et al*. 2016; Löfstedt *et al*. 2016). Hence much of the text included in this paper is repeated here (also *see* Appendix F).

Third, the surveys examined respondents' perspectives on multiple sources of medicines information (e.g. the media, the Internet, pharmacies, medical journals, etc.), which are expected to convey the results of CSRs re-analyses indirectly (i.e. transparency 'intermediaries'). This includes questions on how useful and trustworthy intermediaries are in conveying benefit-risk information. To be clear, these questions were considered especially important in a new environment where medical researchers, in particular, are expected to convey the results of re-analyses to patients and doctors through non-regulatory information channels.

Fourth, the surveys examined respondents' opinions on receiving medicines information that has not been verified by the regulators (e.g. re-analyses conducted by external medical researchers). This includes their opinions on whether the regulators should review re-analyses before or after they are conveyed to the public and how patients might respond to receiving the results of re-analyses from intermediaries. For example, the surveys analysed whether the public *should* be given unverified medicines information that has not been reviewed first by the regulators and how patients say they intend to *react* to receiving such information.

(7.1) Quantity of publicly available information

Two questions measured respondents' opinions on the quantity of information available to the public (that is, at the time of the survey). The first question measured general opinions on receiving more safety information on medicines. The majority of patients (80%) and doctors (56%) 'strongly' or 'somewhat' agreed that 'patients receiving more information on the safety of medicines would increase their confidence in taking medicines' (Table 7.1), although doctors were significantly less likely to indicate so (mean differed between doctors and patients at $p < 0.001$ with independent samples t-test).

Table 7.1: The extent to which patients and doctors agreed or disagreed with the statement: Patients receiving more information on the safety of medicines would increase their confidence in taking medicines

	Patients (%)	**Doctors (%)**
Strongly agree	39	13
Somewhat agree	41	43
Neither agree nor disagree	17	26
Somewhat disagree	2	13

Strongly disagree	0	4
Don't know	1	1

The second question also measured respondents' opinions on the quantity of publicly available medicines information (Table 7.2). The most common opinion for both patients (42%) and doctors (50%) was that there is currently 'an appropriate amount' of information publicly available. However, patients were more likely than doctors to say that there is 'too little' information (+7%) and doctors were more likely than patients to say that there is 'too much' information' (+15%) (Table 7.2).

Table 7.2: Patient and doctor responses to the question: "Would you say that the amount of information about medicines currently publicly available is too much, the appropriate amount, or too little?"

	Patients (%)	**Doctors (%)**
Too much	12	27
Appropriate amount	50	42
Too little	39	32

(7.2) Quality of publicly available information

Respondents indicated the extent to which they agree or disagree with various statements about the medicines and health information that they receive. Three questions measured opinions on the influence of politics and mainstream media, as well as health information bias in general (Figure 7.1). Specifically, respondents were asked whether they agree or disagree with the following statements:

1. Health information for the general public is generally unbiased
2. Politics affects what health information is communicated to the general public
3. Mainstream media sensationalises health information

The large majority of patients (69%) and doctors (83%) 'strongly' or 'somewhat' agreed that 'politics affects what health information is communicated to the general public'. The majority of patients (63%) and doctors (83%) 'strongly' or 'somewhat' agreed that 'mainstream media sensationalises health information'. Doctors were significantly more likely than patients to agree with both of these statements (mean differed between doctors and patients at $p < 0.001$ with independent samples t-test). Doctors (20%) were also significantly less likely than patients

(36%) to strongly or somewhat agree that 'health information for the general public is generally unbiased' (mean differed between doctors and patients at $p < 0.001$ with independent samples t-test).

A further four questions measured opinions on how well medicines and health information is communicated to the public including the clarity of those communications (Figure 7.2). Specifically, respondents were asked whether they agree or disagree with the following four statements:

1. There is a health information communication process in place to communicate with the general public effectively
2. Health information facts are communicated properly
3. Health information communicated to the general public is easy to understand
4. Health communications are generally clear

Patients were significantly more likely than doctors to 'strongly' or 'somewhat' agree with all four statements (mean differed between doctors and patients at $p < 0.001$ with independent samples t-test). First, patients (50%) compared to doctors (38%) were significantly more likely to 'agree that 'there is a health information communication process in place to communicate with the general public effectively'. Second, patients (44%) compared to doctors (28%) were significantly more likely to agree that 'health information facts are communicated properly'. Third, patients were also significantly more likely to agree that health information communicated to the general public is easy to understand (49% vs. 37%) and that health communications are generally clear (46% vs. 34%).

(7.3) Awareness of regulatory bodies and their activities

Two questions measured respondents' awareness of two regulatory authorities: the EMA and their relevant NCA (i.e. MHRA [UK], BfArM [Germany], ANSM [France] or AEMPS [Spain][64]) (Table 7.3). While the vast majority of doctors self-reported that they had heard of their relevant NCA (94%), fewer (80%) said the same about the EMA. Although this means that the large majority of doctors indicated that they had heard of both regulatory authorities,

[64] *see* Table 4.9 to view the agencies' full English names

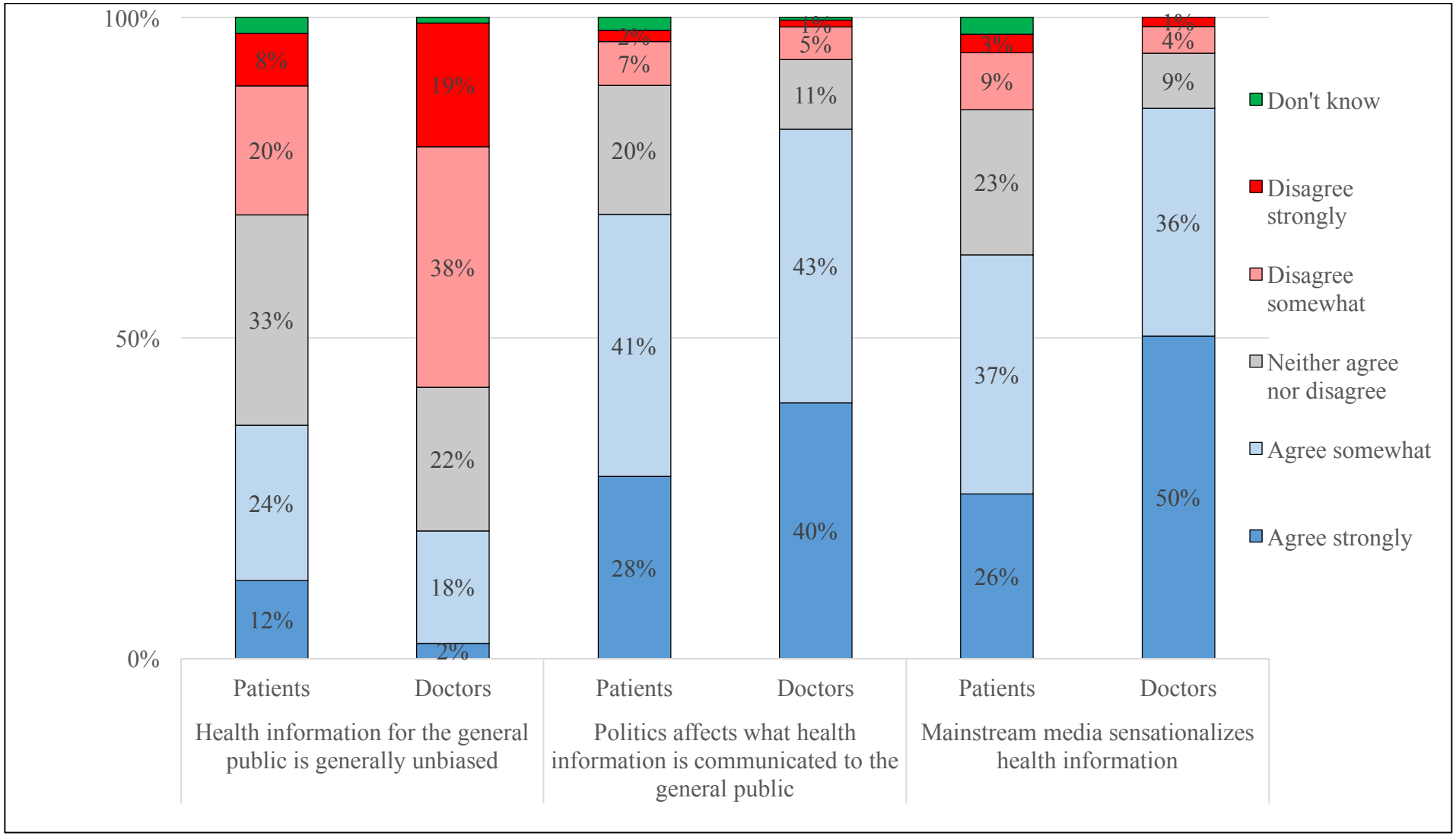

Figure 7.1: Bar chart comparing the extent to which patient (N=1,010) and doctor (N=1,005) respondents agree or disagree with three statements regarding information about medicines and health information.

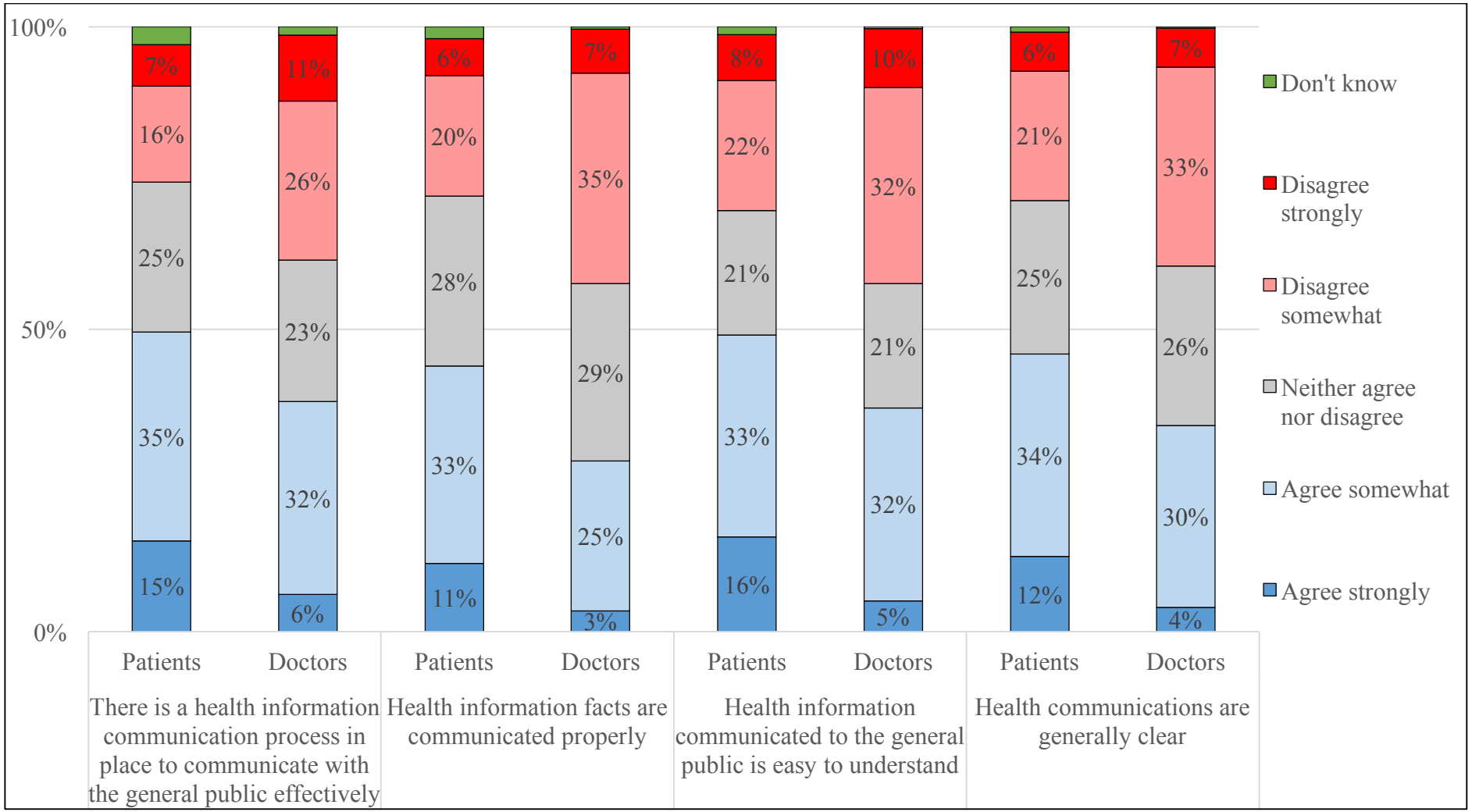

Figure 7.2: Bar chart comparing the extent to which patients (N=1,010) and doctors (N=1,005) agree or disagree with four statements regarding information about medicines and how that information is communicated.

it also means that 6% and 20% of doctors respectively indicated that they have not heard of their relevant NCA or EMA. For patients, the majority said 'no' they have not heard of either their NCA (56%) or EMA (67%).

Table 7.3: Comparison of patient and doctor responses to two questions referring to their relevant NCA and EMA: Have you heard of the [EMA/NCA]? NCAs for each survey country were the MHRA (UK), BfArM (Germany), ANSM (France) and AEMPS (Spain).

	Response	Patients	Doctors
National Competent Authority	*Yes*	44%	94%
	No	56%	6%
European Medicines Agency	*Yes*	33%	80%
	No	67%	20%

Two follow-up questions measured respondents' self-reported awareness of the current communication and information provision activities of both agencies (Table 7.4). Over 75% of patients and doctors said 'no' they were not aware of any specific pieces of information about medicines or health alerts, or health communication activities that either EMA or their relevant NCA are involved with (at the time of the survey) (Table 7.4).

Table 7.4: Comparison of patient and doctor responses to two questions referring to their relevant NCA and EMA: Are you aware of any specific pieces of information about medicines or health alerts or health communication activities that [relevant NCA or EMA] is involved with at the present time? NCAs for each survey country were the MHRA (UK), BfArM (Germany), ANSM (France) and AEMPS (Spain) (Table 4.9).

	Response	Patients	Doctors
National Competent Authority	*Yes*	18%	22%
	No	82%	78%
European Medicines Agency	*Yes*	21%	12%
	No	79%	88%

(7.4) Knowledge of how the regulators assess medicines

One question measured respondents' knowledge of how EMA and their relevant NCA assesses the safety of medicines (Figure 7.3). Specifically, respondents were asked two questions (i.e. one question for NCAs and one question for EMA) on whether they agree or disagree with the following statement:

I have good knowledge of how [NCA/EMA] assesses the safety of [INSERT medical condition] medicines

For EMA, only 17% of doctors and 21% of patients self-reported that they 'strongly' or 'somewhat' agree that they 'have good knowledge of how EMA assesses the safety of medicines'. Rather, over 50% of doctors and patients indicated that they 'strongly' or 'somewhat' disagree with the statement or that they 'don't know'.

For their relevant NCA, almost a quarter of patient (24%) and doctor (25%) respondents indicated that they 'strongly' or 'somewhat' agree that they have good knowledge of how their NCA assesses the safety of medicines. 42% of doctors and 48% of patients indicated that they 'strongly' or 'somewhat' disagreed with the statement or that they 'don't know'.

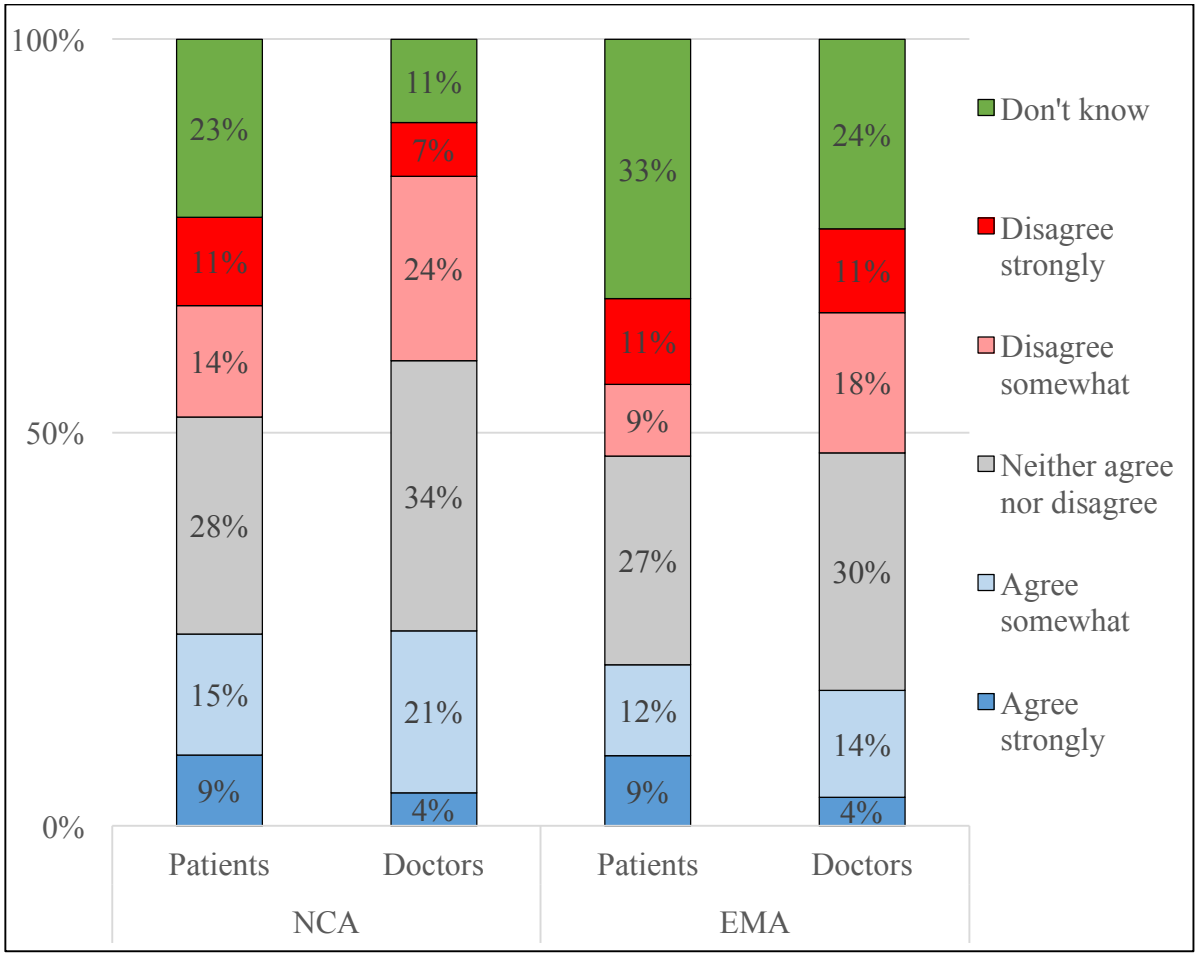

Figure 7.3: Bar chart comparing the extent to which patient and doctor respondents agree or disagree with the statement 'I have good knowledge of how [NCA/EMA] assesses the safety of [medical condition] medicines'. Separate questions were asked for their relevant NCA and EMA. Each relevant medical condition was piped in where applicable.

(7.5) Intermediaries as information providers

A battery of 15 (patients) and 16 (doctors) questions examined how easy respondents find it to obtain medicines advice from different sources of information (i.e. intermediaries) (Figure 7.4). The three most popular sources for patients, rated most frequently as either 'very' or 'somewhat' easy by the majority, were their pharmacy (70%), the Internet (in general) (68%) and their doctor (66%) (Figure 7.4A). In contrast, politicians (19%), EMA (34%) and their relevant NCAs (37%) were viewed as the three least easy sources to obtain medicines information. Thus patients appear to find it easier to obtain information about medicines from the media (e.g. newspapers, television, and/or radio) (43%), a friend or relative (not medically qualified) (43%), and social media (e.g. Facebook or Twitter) (42%) than either EMA or their NCA.

For doctors, the three most popular sources for obtaining medicines information, rated most frequently as 'very' or 'somewhat' easy, were medical journals (85%), colleagues (83%), and the Internet (in general) (81%) (Figure 7.4B). Doctors viewed politicians (8%), friends or relatives (that are not medically qualified) (32%), and social media (34%) as the three least useful sources for obtaining medicines information out of the 16 examined. They were also more likely than patients to say their NCA (68%) and the EMA (52%) were easier sources for obtaining medicines information.

A second battery of 15 (patients) and 16 (doctors) questions examined how trustworthy respondents believe the same sources are in providing them with advice on the side effects associated with specific medicines (Figure 7.4). The two most trusted sources of information for patients, rated most frequently as ''very' or 'somewhat' trustworthy, were their doctors (78%) and the pharmacy (75%) (Figure 7.6A). For doctors, the most trustworthy sources of information were medical journals (90%), their NCAs (86%) and the EMA (83%) (Figure 7.4B). For both patients and doctors, politicians, social media, and the mass media (e.g. newspapers, television, and/or radio) were viewed as the least trustworthy sources of medicines information.

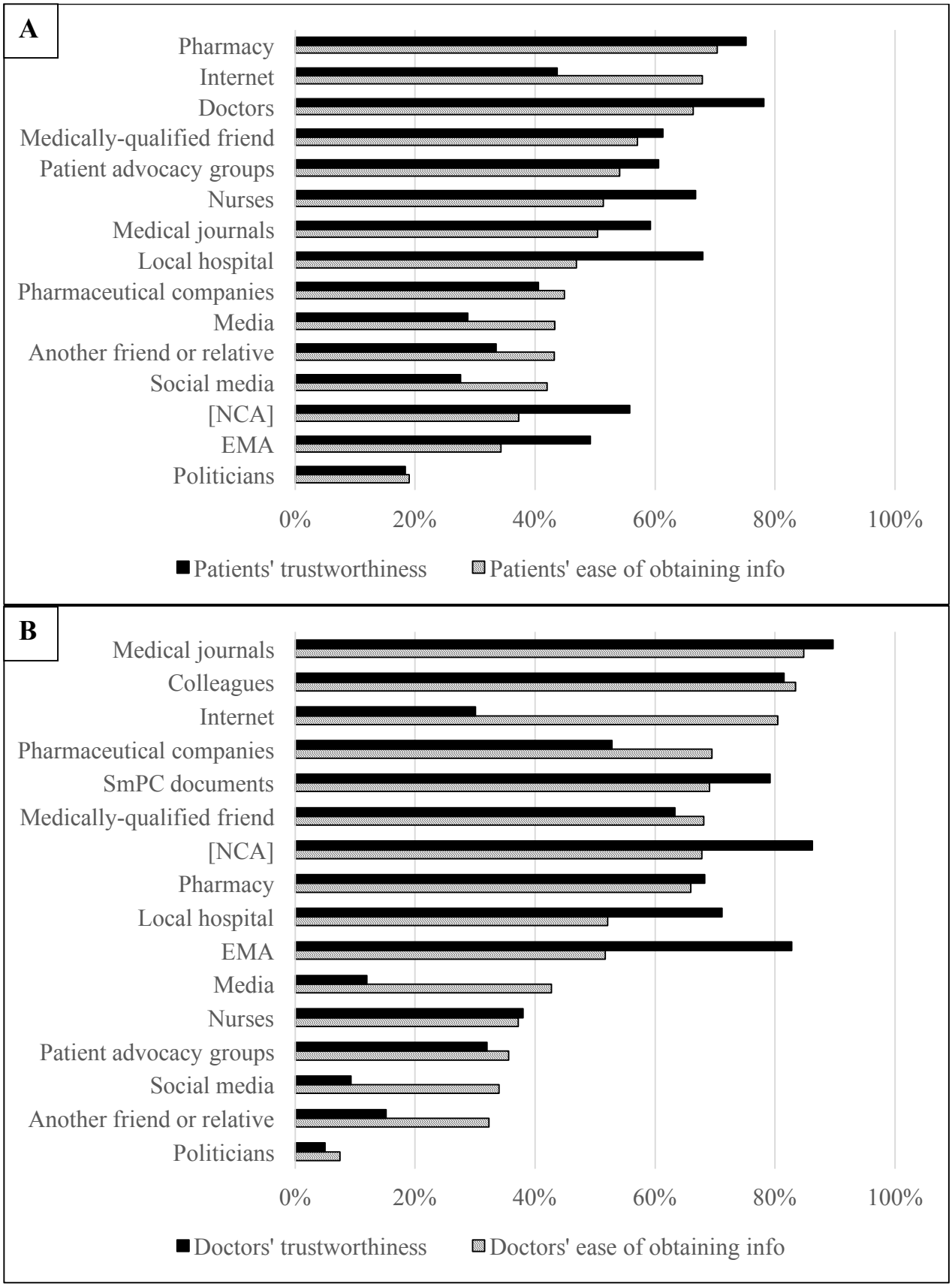

Figure 7.4: Bar charts for (A) patients and (B) doctors that compare: (1) respondents (%) that indicated 'very easy' or 'somewhat easy' to the question: "How easy is it for you to obtain information about medicines from each of the following sources of information?" (light shading) and; (2) respondents (%) that indicated 'very trustworthy'

or ‘somewhat trustworthy’ to the question: “How trustworthy do you believe the following sources are in providing you with advice on the side effects associated with specific medicines?” (dark shading). Results are sorted by ease of obtaining information (light shading). SMPC denotes summary of product characteristics.

(7.6) When new findings should be made publicly available

Two questions measured *when* respondents think that information on the safety of medicines *should* be made publicly available. In particular, the questions examined opinions on whether unverified safety information (e.g. results from CSRs re-analyses) should be conveyed to the public. The first question provided four possible options for when respondents think that information should be conveyed to the public about a possible safety issue with a medicine that they use or may use (Figure 7.5). Just over half (51%) of patient respondents indicated that this information on their medicines should be conveyed ‘when there is a possible sign of a safety problem’ over all other options (Figure 7.5). Far fewer patient respondents indicated that this information should be conveyed after the issue has been investigated first. This includes the options ‘when the problem has been investigated and it is not clear whether the issue is related to the medicine’ (21%), or after it has been investigated by the (relevant) pharmaceutical company (13%) or the regulators (14%) and these actors believe the problem is related to the medicine.

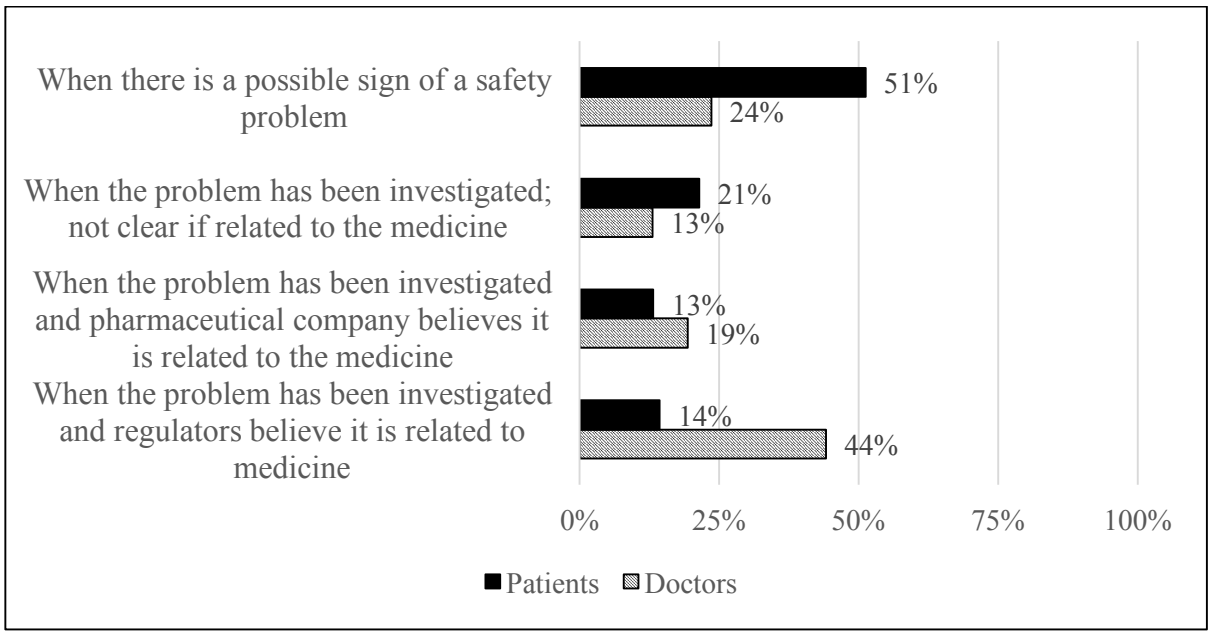

Figure 7.5: Bar chart comparing answers to the question “At what stage do you think information should be conveyed to the public about a possible safety issue of a medicine that they use or may use?”.

In sharp contrast, the most popular response for doctors was that information about a possible safety issue should be conveyed to the public *after* it has been investigated and *the regulators* believe the problem is related to the medicine (44%). Less than a quarter (24%) of doctor respondents indicated that information should be conveyed to the public 'when there is a sign of a safety problem' (Figure 7.5). Patients differed significantly from doctors over when this safety information should be conveyed on all four response options ($p < 0.001$; using pairwise comparisons in a generalised linear model with a binomial distribution, logit link function, and doctor/patient as a factor variable).

The second question asked respondents to indicate whether they think it is a 'good idea' or a 'bad idea' to inform the general public before a scientific analysis has been completed[65]. 'Scientific analysis' was clarified to mean "a full review of the available data by the regulators and pharmaceutical industry". In line with the previous question, patients (60%) were more likely than doctors (24%) to indicate they think it is a 'good idea' to inform the general public before a scientific analysis is completed, with a concomitant number of patients (40%) and doctors (76%) indicating they think it is a 'bad idea'.

(7.7) Patients' reactions to receiving safety information

One question measured respondents' behavioural intentions[66] after receiving potentially adverse safety information relating to a medicine they are currently taking. Indeed, although patients may be unware of its original source, this information could come from re-analysed CSRs results suggesting their medicine is less safe than was previously thought. After personally receiving (e.g. via letter, telephone, e-mail etc.) information that points to safety problems with a medicine they are currently taking (i.e. information contradicting its safety profile), the most popular behavioural intention for patients was to either: 'seek additional advice about the medicine' (56%) or 'stop taking the medicine' (26%) (Figure 7.6A). A further 8% of respondents indicated they would 'reduce their dose of their medicine', while others indicated they would 'continue to take their medicine as usual' (9%) or said 'don't know' (4%) (Figure 7.6A).

[65] "Overall, do you think it is a good idea or a bad idea to inform the general public **before** a scientific analysis is complete? (By scientific analysis, we mean a full review of the available data by the regulators and pharmaceutical industry" (Yes/No).
[66] In other words, respondents' perceived likelihood of engaging in a given behaviour.

There were also notable variations between different nations and geographic regions on the combined likelihood respondents would stop taking and reduce the dose of their medicine (Figure 7.6B). This ranged from 8% of respondents in the South West of England and Wales, to 54% in the North-East of France indicating they would stop taking or reduce the dose of their medicine.

Several statistically significant differences also emerged between respondents on the combined 'stop' and 'reduce' variable when the sample was stratified based on respondents' nation and medical condition (in a generalised linear model with sequential Bonferroni corrections for multiple comparisons)[67] (Figure 7.7). The number of patients reporting that they would stop or reduce – i.e. the combined percentage of respondents across those two response options – in the UK sample differed significantly from all other groups at $p < 0.001$ (Figure 7.5). There were no significant differences between any other national samples on these combined response categories at $p < 0.05$. In terms of differences across medical conditions, the number of patients reporting that they would stop or reduce their dose in the HIV/AIDS group differed significantly from patients with all other medical conditions included in the survey at $p < 0.01$ (Figure 7.7). There were no significant differences in the results from patients with any other medical condition at $p < 0.05$.

(7.8) Doctors' opinions on improving regulatory communication

Doctor respondents were also asked an additional open-ended question about what they think would be the best way for regulators to communicate medicines information better and more effectively with their patients (Table 7.5). Respondents provided a wide variety of answers that were coded into nine categories across all four sample countries. They could provide more than one suggestion and an average of 288 suggestions were made in the UK (323), Germany (252), Spain (293), and France (282).

[67] Generalised linear models with a binomial distribution and logit link function are a means for assessing the effect of categorical and/or continuous variables on a dichotomous outcome variable. Nations were included in the sample as the multiple nominal independent variable to examine differences in the response variable across nations. Bonferroni corrections for multiple comparisons are a conservative approach to correcting for the increased possibility that chance alone could lead to significant findings when conducting multiple pairwise comparisons (e.g. between values on the outcome variable for each nation).

Table 7.5: Coded doctor responses to the open-ended question: "Based on your medical experience, what would be the best way for regulators to communicate medicines information better and more effectively with [medical condition] patients?" Each relevant medical condition was included for speciality doctors (e.g. multiple sclerosis) or left blank for GPs. The percentages show the average of all suggestions for each country and then overall for all countries.

	UK	Germany	Spain	France	Average
Information should be communicated face-to-face with doctors and/ or other healthcare professionals	24%	22%	29%	29%	**26%**
Information should be communicated simply and in a comprehensible way to patients	15%	13%	17%	6%	**13%**
Develop more trusted official websites	9%	11%	7%	9%	**9%**
Do not release information until it has been fully investigated by regulators	7%	8%	11%	5%	**8%**
Improve and/or use the news media	7%	11%	4%	4%	**7%**
Send e-mails, leaflets and/or newsletters directly to patients	8%	6%	5%	7%	**6%**
Convey information through trusted third parties (esp. patient groups)	6%	3%	4%	12%	**6%**
Other suggestions made by <5% (e.g. create visuals, make engaging TV programmes, utilise social media)	17%	13%	13%	16%	**15%**
No answer or Don't know	7%	13%	10%	12%	**10%**
Number of suggestions made*	323	252	293	282	**288**

*respondents could provide more than one suggestion.

The most popular answer that accounted for 26% of all suggestions was that medicines information should be primarily communicated face-to-face by doctors and other healthcare professionals (Table 7.5). Reflecting the sentiments of these respondents, one UK doctor commented:

> *"[Information should be communicated]…via Clinicians/Nurses/Healthcare Professionals with whom they have a relationship and can explain to them what the new information is with respect to the individual medication"*

Or as another suggested:

> *"I think it would be better [for the regulators] not to communicate information to patient[s] at all. It would be better to [use] the patients' doctors who can then interpret*

the details and explain the facts in lay person terms. This information would be better received by the patients from someone they know and trust."

The second most popular suggestion that accounted for 13% of all responses was that medicines information should be communicated simply and in a comprehensible way to patients (Table 7.5). For example, a respondent from Germany commented:

"Factual information belongs in the hands of professionals, patients need a simple summary that better explains the relations: Laymen need Laymen information"[68]

Or as a UK respondent stated:

"The results should be analysed and peer reviewed by a trustworthy external body and communicated clearly to the public in plain English. Results need to be put into context i.e. numbers needed to harm and numbers needed to treat. Leaking raw data into the public domain is likely to be harmful".

The third most popular suggestion that accounted for 9% of all suggestions was that the regulators should develop their websites to provide a trusted and easily accessible source of information for patients. Other less frequently mentioned suggestions were that information should not be released until it has been fully investigated by the regulators (8%) and that the regulators should improve and/or use the news media (7%), send e-mails, leaflets and/or newsletters directly to patients (6%), and convey information through trusted third parties (especially patient groups) (6%). For example, one UK respondent commented:

"Not through the Daily Mail! Clearly presented safety data to health care professionals, can then be disseminated to [the] patient population. Info should be available in a patient friendly manner on approved websites."

Other individual suggestions were also made that accounted for less than 5% of all responses. These include suggestions such as that the regulators should create better visuals (e.g. to communicate statistical information more effectively), make engaging TV programmes (e.g. about medicines), and utilise social media.

[68] Fachinformationen gehören in Fachhände, Patienten benötigen eine einfachere Zusammenfassung, welche die Zusammenhänge besser erklärt: Laien benötigen Laieninformationen

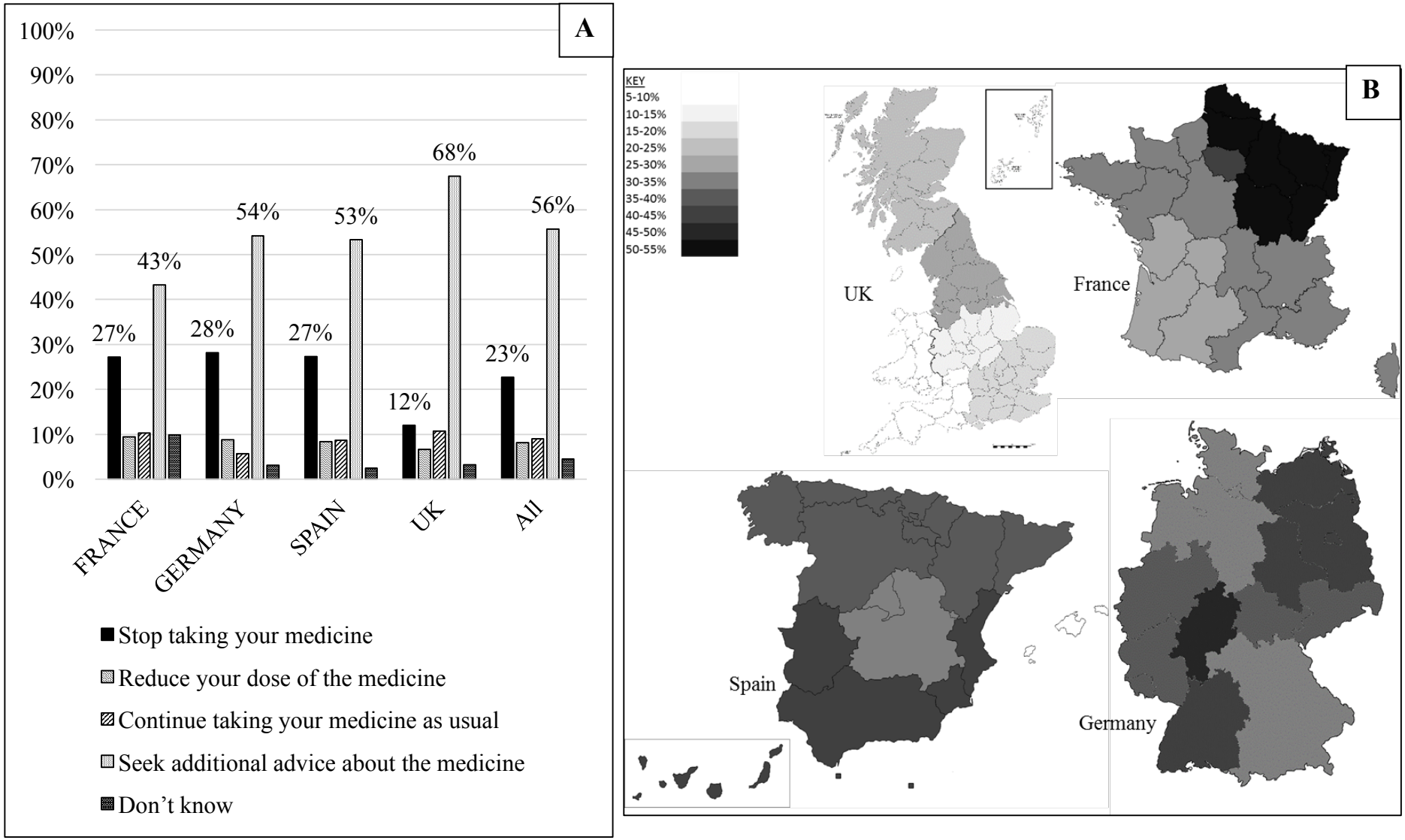

Figure 7.6: (A) Respondents' answers (%) to the question: "If the information you personally received (via letter, telephone, e-mail etc.) points to safety problems with a [insert sample group medical condition] medicine you are currently taking, do you think you are more likely to…" (N=1010). (B) Four choropleth maps comparing regional variations for patients that indicated 'stop taking your medicine' or 'reduce the dose of your medicine'. The darker the shading the higher the number of respondents in that geographic region that indicated stop or reduce (see key).

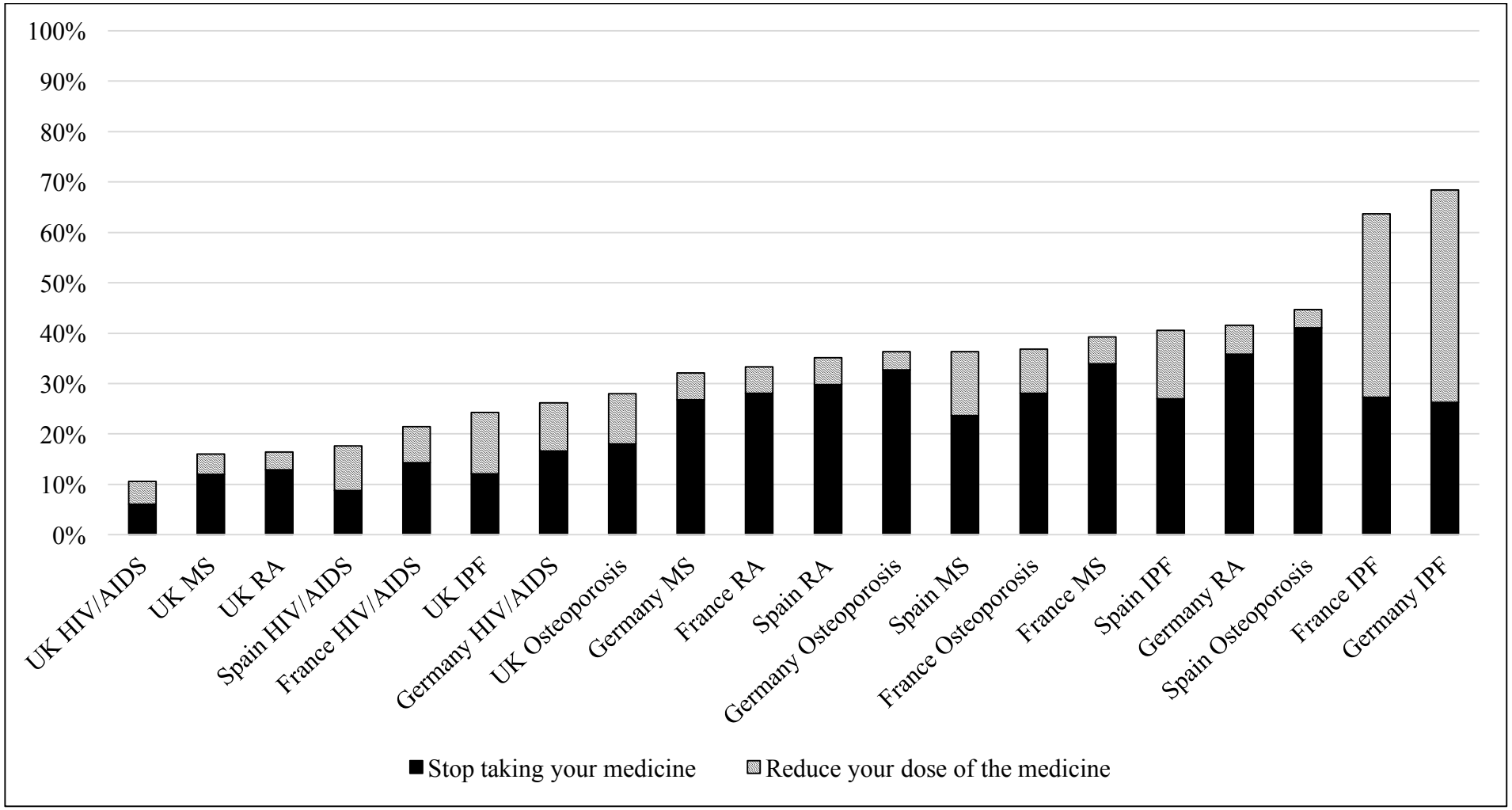

Figure 7.7: Bar chart comparing respondents divided into country and medical condition groups that answered either reduce your dose of the medicine (light shading) or stop taking your medicine (dark shading) (%) for the question: "If the information you personally received (via letter, telephone, e-mail etc.) points to safety problems with a [relevant medical condition] medicine you are currently taking, do you think you are more likely to… (a) stop taking your medicine, (b) reduce your dose of the medicine, (c) continue taking your medicine as usual, (d) seek additional advice about the medicine or (d) don't know". Medical condition abbreviations: MS = Multiple Sclerosis; RA = Rheumatoid Arthritis; IPF = Idiopathic Pulmonary Fibrosis. (N=1010).

Chapter VIII: EVALUATION OF EMA's TRANSPARENCY POLICIES

This chapter evaluates the case study evidence on the effectiveness of EMA's transparency policies. While the previous three chapters presented and analysed evidence from multiple perspectives (Chapters V-VII), in this chapter a full discussion of the strengths and weaknesses of EMA's input transparency policies and overall strategy for enhancing transparency is provided. In particular, the case study evidence can be used to answer directly and explicitly the research question by addressing how effective EMA's transparency policies have been in achieving its public policy objectives. This will also enable a fully informed discussion of the main implications of the EMA case study for the broader literature on transparency in risk regulation.

The chapter proceeds as follows. First, the case study evidence is used to identify and explain the most significant changes to EMA's transparency strategy between 1995 and 2016. Three salient changes are identified using the typology of transparency in risk regulation (Chapter II) and explained drawing primarily on the historical analysis (Chapter V). Second, the case study evidence is used to evaluate the effectiveness of clinical trial registration and summary level results reporting for the medical research community, patients, and doctors. In particular, the section evaluates the strengths and weaknesses of each of EMA's policies and their effectiveness in achieving EMA's transparency goals. Third, an evaluation of the effectiveness of EMA's CSRs transparency policies in enabling the medical community to conduct re-analyses of input data is provided. The section focuses on quantity and quality issues, the capacity of medical researchers to re-analyse CSRs and the effects of enabling re-analyses. Fourth, the survey results are discussed in order to evaluate the effectiveness of EMA' CSRs transparency policies for patients and medical doctors.

(8.1) EMA's transparency strategy post-2010

Between 1995 and 2016, EMA made significant changes to its transparency strategy (Chapter V). This includes changes to what regulatory events and processes the regulators wanted to make more transparent (objects), how (mechanisms), why (goals), and for whom (audiences) (Chapter II). One of the most important changes centred on which transparency objects the regulators sought to make more transparent to those outside the traditional regulatory network.

In particular, EMA developed and introduced an unprecedented wave of new *input* type policies immediately after the ombudsman's 2010 decisions (Chapter V). The most notable polices were to implement a new reactive access to documents policy (EMA, 2010a); launch EMA's own publicly accessible online clinical trials register (EMA, 2011b); enable sponsors to upload summary level trial results onto the register (EMA, 2013, 2014dd); establish a publicly accessible web-portal for viewing a sub-set of suspected adverse reaction data (i.e. data on possible side effects) (EMA, 2012c); and, most significantly, EMA became the first pharmaceutical regulatory agency in the world to publish CSRs online proactively (EMA, 2014a, 2014b) (Chapter VI). Broadly speaking, these sought to enhance the transparency of the data and information that underpins decision-making in EMA's scientific committees (Bonini *et al*. 2014; EMA, 2015a) (Chapter V).

Introducing this unprecedented wave of input policies was a significant change for EMA. Although the regulators had already been committed to transparency for 15 years (Sauer, 1998; EMA, 2009), until 2010 they had not introduced any input policies (Chapter V). Rather, the regulators had previously focused on enhancing the transparency of decision-making outputs (e.g. European Public Assessment Reports) (Sauer, 1997; Lekkerkerker, 2005) and procedural processes (e.g. standard operating procedures) (EMA, 2000a, 2005c, 2009). It is true to say that EMA also introduced several new operational transparency policies between 2010 and 2016 such as publishing meeting minutes online (EMA, 2012b, 2014e) and introducing patient representatives onto scientific committees (EMA, 2017l). However, the most significant change and the regulators' main focus was on developing and introducing a multiplicity of new input type policies.

A second salient change to EMA's transparency strategy centred on *how* the regulators sought to enhance transparency (i.e. transparency policy mechanisms) (Chapter VI). In particular, EMA shifted from a reactive to a much more proactive approach (Chapters V and VI) (EMA, 2012b, 2014a, 2014b). Shortly after the ombudsman's 2010 decisions (Ombudsman 2010a, 2010b), EMA immediately introduced a new reactive transparency policy, which enabled the regulators to meet its legal requirements and provide outsiders with access to documents on a case by case basis (i.e. on request) (EMA, 2010a; Ombudsman, 2011). This rapidly changed after a milestone 2012 announcement (*see* EMA, 2012a), after which EMA began developing numerous new proactive input transparency policies (EMA, 2011b, 2014b, 2014d). While the

new proactive approach started with the publication of relatively small quantities of data (e.g. summary level trial results) (EMA, 2011b, 2012c), the regulators began incrementally publishing increasingly larger quantities of data and information online (e.g. CSRs with thousands of pages) (EMA, 2014b). Therefore the mechanisms for EMA's transparency policies trended towards publishing as much data and information as feasibly possible online (Rasi, 2012). There is also clear evidence that EMA want to continue this trend such as with the proposed proactive publication of hundreds of thousands of pages of individualised patient level data (EMA, 2016), although the regulators make clear that there are challenging issues that need to be resolved before doing so (e.g. data anonymisation and patient privacy) (Koenig *et al*. 2014; EMA, 2014b, 2017k). EMA's input transparency policy mechanisms therefore trended from a reactive case-by-case approach to the proactive publication of enormous and increasingly large quantities of data online.

A third salient change to EMA's transparency strategy centred on the goals and connected audiences of the agency's input policies (Chapter V). In particular, the regulators' became increasingly fixated on enhancing input transparency for the benefit of medical researchers from outside the traditional regulatory network (i.e. changes to policy goals and audiences) (Chapter V). During its first 15 years, the main goals of EMA's policies were to ensure the agency was independent from the Commission, industry, and national regulatory authorities (Sauer, 1998; EMA, 2005a) and to communicate clearly and effectively with its many stakeholders including patients and healthcare professionals (EMA, 2005a; 2009) (Chapter V). This can be most clearly seen with the agency's incremental "step-wise" introduction of procedural process and output type policies (EMA, 2009: 1), which were viewed as a useful means for "subjecting the agency's activities to effective public auditing" (EMA, 1996) and communicating effectively with patients and healthcare professionals by providing "useful, clear and comprehensive information" (EMA, 2005a).

However, since the ombudsman's 2010 decisions the regulators have become increasingly occupied by significant external pressure from external medical researchers. Although numerous goals of different EMA input policies can be clearly identified (e.g. minimising dissemination biases and better connecting trialists with patients) (Chapter VI), the regulators were primarily occupied by the most radical goal of enabling medical researchers (and others) to 'independently' re-analyse CSRs (EMA, 2013a, 2014f; Eichler *et al*. 2012, 2013; Bonini *et*

al. 2014). In turn, the regulators expected to achieve at least four secondary goals for the medical community and indirectly provide patients and healthcare professionals with a better understanding of the benefits and risks of medicines (Chapter VI). Therefore there is clear evidence that, since 2010, EMA regulators have become increasingly fixated on the challenging goal of enabling medical researchers to re-analyse clinical trial data. In so doing, the agency placed much less emphasis on the objectives of independence and benefit-risk communication than it had in previous years (that is, at least with regards to the regulators' transparency policies) (Chapter V).

(8.2) Registration and summary-level results policies

This section evaluates the effectiveness of the first two EMA input transparency policies in achieving the regulators' public policy objectives. These are registering clinical trials through establishing an online register called EU-CTR (clinicaltrialsregister.eu) (EMA, 2011b) and enabling sponsors to upload summary level clinical trial results onto that register (EMA, 2012c). At least seven main objectives of these two policies were identified for the medical research community (e.g. medical researchers and clinical trialists) (Chapter VI). The two most important are (1) to provide a way of finding basic information on trials and their results (Viergever and Li, 2015) and (2) to improve the issue of nonpublication and associated biases (Chan *et al*. 2014). Two main objectives for patients and doctors were also identified (Chapter VI). These are (1) to better connect patients (and their doctors) with trialists (Dickersin and Rennie, 2001) and (2) to inform patients and doctors about the results of clinical trials (Chan *et al*. 2014).

One of the greatest strengths of these two input transparency policies is that the main mechanism for achieving transparency, EU-CTR, provides a high-level of technical functionality and capacity (EMA, 2011b, 2017i; WHO, 2017). The online web-portal enables summary level results to be uploaded (EMA, 2013c) and meets the WHO's strict criteria including on "content, quality and validity, accessibility, unique identification, technical capacity and administration" (WHO, 2017). This level of functionality is essential for providing a place where all trialists, within EMA's jurisdiction, can register a clinical trial and upload summary level results. EU-CTR is also free to use and publicly accessible online (EMA, 2017i). This means that all audiences of EMA's policies can receive the information they need,

which is an essential pre-requisite for achieving the regulators' goals (e.g. to conduct systematic analyses, find basic trial information, or inform patients and doctors about clinical trials) (Viergerver and Li, 2015). There is also clear evidence that the medical research community – but not necessarily doctors and patients – have the capacity to process, digest, and use the information contained in trial registers including summary results (Song *et al*. 2010; de Wetering *et al*. 2012; Freshwater *et al*. 2013; Miller *et al*. 2015; Chen *et al*. 2016). For example, medical researchers have used trial results for many years in order to conduct systematic reviews (Ioannidis, 2005), which are considered by many as the "gold standard" of evidence on medicines (Dickersin and Rennie, 2003; Doshi *et al*. 2012).

However, there are also several significant weaknesses of EMA's two input transparency policies that significantly limit their effectiveness for all audiences. One of the most important issues is that EU-CTR does not contain the desired quantity of registered clinical trials or reported summary-level results needed for fully achieving any of the regulators' goals. In particular, there has been a distinct lack of compliance with registration and results reporting from clinical trialists (Song *et al*. 2010; Prayle *et al*. 2012; Miller *et al*. 2015; Viergerver and Li, 2015; Chen *et al*. 2016). This is an issue because all trials need to be registered and reported in order to achieve the highest level of effectiveness. For example, the goals of providing basic trial information, better connecting trialists with patients, and mitigating dissemination biases are dependent on trialists registering and reporting results on EU-CTR (Chapter VI). In turn, this non-compliance issue has *a priori* limited the effectiveness of EMA's two policies in achieving its secondary goals such as reducing the wastage of scientific resources, reducing unnecessary harm to patients, and improving systematic reviews.

A second weakness of EMA's policies is that they are focused too narrowly on tackling non-compliance through mandatory reporting. Similar to the FDA, EMA's main mechanism for improving compliance has been to mandate that sponsors post trial results on EU-CTR either six months or one year after trial completion or premature termination (EMA, 2014d). There is some evidence that this will result in reducing non-compliance such as for industry sponsored clinical trials (i.e. trialists that have the capacity and incentives to register and report) (Rawal and Deane, 2015). However, a significant issue with mandatory reporting is that it is unlikely to address some of the underlying reasons for non-compliance (Bian and Wu, 2010). This includes trialists not being aware of reporting or its importance; resource constraints for

registering and reporting (e.g. a lack of time); unclear regulatory responsibilities among trialists; a lack of incentives and many others (Chapter VI) (Law *et al*. 2011; Smyth *et al*. 2011; Weber *et al*. 2015; Viergerver and Li, 2015). There is also clear evidence that other policies are likely to be much more effective in tackling non-compliance (Bian and Wu, 2010). Therefore, the regulators will need to implement measures beyond mandating registration and results reporting in order to achieve EMA's ultimate transparency goals for all audiences, (Viergerver and Li, 2015). This will require first to fully understand and address the underlying reasons why many trialists do not register and report results such as by conducting in-depth empirical research on the perspectives of trialists (Scherer *et al*. 2015).

A third weakness of EMA's input transparency policies is that mandatory reporting only applies to trials conducted in the EEA and EU member states (EMA, 2014d). As a decentralised EU agency, EMA cannot mandate clinical trial registration and results reporting outside of its jurisdiction. Yet, the issue of non-compliance is a global issue (Wager and Williams, 2013; Viergerver and Li, 2015; Zarin *et al*. 2015). Although mandatory reporting can improve rates in Europe, there are significant issues of non-compliance across the world including notable regional variations. In turn, these global issues have weakened the effectiveness of EMA's transparency policies in achieving its goals. This is because all audiences of input transparency need clinical trial information not just from EMA jurisdiction countries (e.g. to obtain basic trial information or mitigate dissemination biases). Therefore the regulators need to widen the scope of their policies beyond their jurisdiction in order to improve the effectiveness of their policies. This will necessarily require working more closely with other regulatory authorities across the world on issues of non-compliance, which is essential if the regulators' want to achieve the ultimate goals of their transparency policies.

Beyond these transparency *quantity* issues, one of the most significant weaknesses of these two policies is that they do not meet the desired information *quality* needed to achieve the regulators' goals. All audiences of EU-CTR need high quality information (Laine *et al*. 2007; Viergerver and Ghershi, 2011; Viergever *et al*. 2014). If high quality information is not provided then the medical research community, patients and doctors cannot trust or use trial registers. One of the most significant issues is that EU-CTR does not have the same peer review process as medical journals (Science and Technology Committee, 2013). This has resulted in many trial entries being incomplete or of poor quality (Viergever and Ghershi, 2011; Manzoli,

2014). Although trial registers are not expected to meet the quality standards of medical journals, this weakness still significantly affects their reliability and usefulness for all audiences (Viergever and Ghershi, 2011). For this reason, many individuals, groups, and institutions make clear that trial registration should "complement not replace" medical journal reporting (Zarin *et al*. 2011; Science and Technology Committee, 2013). Therefore until the quality of trial registers meets that of medical journals EU-CTR will never be as effective for disseminating trial results.

A second quality issue is that EU-CTR is significantly less useful for doctors than the medical research community. Most prescribing doctors will be able to process, digest, and use information on clinical trials that are registered and reported on EU-CTR (e.g. to inform prescribing or identify recruiting trials) (Tuffs, 2005). Yet, not all doctors will have the time to go through EMA's register in order to review the latest evidence on medicines they prescribe, let alone other registers as well (British Medical Association 2015). What is more likely is that prescribing doctors will continue to use peer review medical journals to inform decision-making (e.g. systematic reviews of the literature). As the survey results showed (Chapter VII), doctors viewed medical journals as their most trustworthy (90%) and useful (85%) source for obtaining medicines information.

A third quality issue is that most patients are unlikely to be able use the information made available in EU-CTR. In contrast to doctors, patients may have more time to access EU-CTR (e.g. to view trials relevant just for their specific medicines). However, most patients are much less likely to be able to understand the results of trials reported in registers (Garcia-Retamero and Galesic, 2013). This includes interpreting results that were originally written for medical researchers and how they fit into their own decision-making context (ibid, 2013). Due to these issues with EU-CTR, the European Parliament introduced layperson summaries for trial results as a way of better communicating results to patients (and participants) (Clinical Trial Regulation EU no. 536/2014). However, recent studies have made clear that even the developing 'layperson' summaries, let alone the original trial entries, may be difficult for patients to understand (e.g. without prior knowledge of the clinical trial process) (Sroka-Saidi *et al*. 2015; Chamberlain-James, 2015; Nottbohm *et al*. 2016). Thus EMA's registration and reporting policies have significant issues that weaken their effectiveness in achieving the regulators' goals for patients and doctors.

(8.3) Re-analysing CSRs

This section evaluates the effectiveness of EMA's CSRs transparency policy in achieving the regulators' public policy objectives for the medical community (e.g. medical researchers, industry, trialists, and health technology assessors). The first overriding goal of the "landmark" policy is to enable the medical community to re-analyse the main inputs used for decision-making in EMA's scientific committee (Bonini *et al*. 2014). In turn, re-analyses conducted by those outside of regulatory agencies are expected to achieve numerous secondary goals (Chapter VI). These include improving the scientific knowledge base on pharmaceuticals (Eichler *et al*. 2013; Bonini *et al*. 2014); overcoming the failure of registration and results reporting (e.g. mitigating dissemination biases) (Wieseler *et al*. 2012; Doshi *et al*. 2013; Muand *et al*. 2014); scrutinising regulatory decisions and interpretations of CSRs (Goldacre, 2012; Chan *et al*. 2014); enabling informed decision-making for non-EMA decision-makers (McGuaran *et al*. 201; IQWiG, 2013; NICE, 2013); improving the efficiency and effectiveness of drug development and the clinical trial process (Eichler *et al*. 2013; GlaxoSmithKline, 2013); and better informing patients and doctors about the benefits and risks of medicines (EMA, 2014a; 2016a) (Chapter VI).

(8.3.1) Desirability and feasibility of full disclosure

One of the main advantages of EMA's CSRs policy for the medical community is that the regulators are releasing high quantities of data needed to enable re-analyses (EMA, 2014a). In particular, the policy seeks to make as much data as possible publicly available from CSRs approved after January 2015 (i.e. after the policy came into force) (EMA, 2014b, 2016a, 2017m). A key approach to achieving such quantities of transparency is the regulators' default position that CSRs should not be considered confidential and so limited redactions should be made (Bonini *et al*. 2014; EMA, 2016d). Providing high quantities of CSR data is highly desired by most re-analysers and is viewed as an important pre-requisite for achieving the regulators' secondary goals (Gøtzsche, 2011; Doshi *et al*. 2013; Chalmers *et al*. 2014). While some have argued that high levels are needed for conducting comprehensive re-analyses (e.g. as otherwise key data might be omitted through redactions) (Wieseler *et al*. 2012; Maund *et al*. 2014), others have argued that enabling *all* outsiders with access to CSRs and not just re-analysers is important (Jefferson *et al*. 2011). For example, enabling anyone that wants to see

CSRs data is considered by some as an ethical requirement in the reliability and reproducibility of scientific research and peer review (e.g. to assesses the quality of re-analyses) (Prinz, 2011; Bohannon *et al*. 2012; Buthe *et al*. 2015). A key strength of EMA's policy, for those expected to re-analyse data at least, is therefore that the regulators have sought to provide large quantities of CSRs data.

However, providing large quantities of CSRs transparency to enable re-analyses has also created significant issues that have limited the effectiveness of the regulators' policy (Chapter VI). In particular, three main issues collectively show that there are complicated and important legal and technical challenges that inhibit the full disclosure of CSRs. The first issue is that EMA's policy only applies to CSRs approved after January 2015 (EMA, 2014b). This means that it does not enable re-analyses of CSRs for any medicines approved before this date (EMA, 2014b). This is primarily due to significant technical and resource issues with disclosing CSRs relating to previously approved medicines (e.g. reviewing enormous quantities of data for possible redactions) (EMA, 2013b). This has significantly weakened the effectiveness of EMA's policy in achieving its secondary goals. For example, for medicines authorised prior to January 2015 biases in the published literature cannot be mitigated and exploratory analyses cannot be conducted.

The second issue is that EMA's policy falls short of providing the most granulated levels of input data, which is referred to as 'patient level data' or the fourth level of clinical trial data transparency (Science and Technology Committee, 2013; Koenig *et al*. 2014). While consulting various stakeholders on its CSRs policy, EMA regulators removed the publication of patient level data from its 2014 policy (Koenig *et al*. 2014). This was primarily due to patient privacy and data anonymisation challenges that would have stalled the release of CSRs (EMA, 2013, 2014). However, by removing patient-level data from EMA's policies the agency admitted that there are limitations to the quantity of data that could be released under its 2014 policy. In turn, limiting the quantity of data made available limits the effectiveness of EMA's policies in achieving its goals. For example, less comprehensive exploratory re-analyses can be conducted (Koenig *et al*. 2014).

The third issue is that not all actors agree with the publication of such large quantities of data desired by many re-analysers (*see* Price II and Minssen, 2015). First, although EMA's policy

makes clear that most data should not be considered confidential (EMA, 2014b; 2016d), CSRs still do contain information that has caused real concerns for some companies about competitors using proprietary information (PhRMA and EFPIA, 2013; Pfizer, 2013; Hunter, 2015). For example, EMA has been sued numerous times for attempting to release CSRs through its reactive access to documents policy (EMA, 2013e; EMA, 2017j). Second, CSRs contain data and information that could result in the identification of individuals (e.g. trial participants or company employees) (EHA, 2013; GlaxoSmithKline, 2013; IFAH-Europe, 2013). Although some argue that this information can simply be redacted, there are concerns that EMA's policy does not sufficiently address complicated issues with data anonymisation (GlaxoSmithKline, 2013; EMA, 2017k). These two issues in particular mean that there are significant restrictions over what information can feasibly be made publicly available and that some audiences of EMA's policies do not agree with full disclosure (Chapter VI). In turn, this reduces the effectiveness of EMA's policies in achieving its goals due to the negative effects of legal action (e.g. resource consumption), restrictions on the quantity of data that can feasibly be made public (e.g. commercially confidential information), and unwanted consequences for industry (e.g. competitors accessing proprietary information).

(8.3.2) Capacity to re-analyse CSRs

A second key advantage of EMA's CSRs policy for the medical research community is that it provides high quality data needed for conducting rigorous re-analyses. While registration and results reporting quality have been strongly criticised (Viergever and Li, 2015), CSRs differ in that they are inherently of high quality as they are written by pharmaceutical companies that have to adhere to strict guidelines for licensing approval (e.g. they follow the International Council for Harmonisation Guidelines) (EMA, 2012d; International Council for Harmonisation, 2017). EMA's policy therefore enables re-analysers to receive high quality information on clinical trial data, which can enable high quality re-analyses to be conducted in the achievement of the regulators' secondary goals. For example, CSRs contain full protocol and protocol amendments information that are not always found in trial registers or medical journals (Maund *et al*. 2014). However, an important subsequent question relating to the quality of published information centres on whether there are receptors capable of processing, digesting and using the information made available (Heald, 2006). This is particularly important because CSRs have traditionally been used for discussions between those within the

regulatory network (i.e. the Commission, industry, and regulatory authorities) and so may be unfamiliar to outsiders (e.g. medical researchers) (Doshi *et al*. 2013).

On the one hand, there is clear evidence that industry has the capacity to re-analyse CSRs. Pharmaceutical companies write and use CSRs for approving their own medicines and so are familiar and up-to-date with changes to their structure and format (EMA, 2012d). There is evidence that industry are interested in conducting re-analyses (Chapter VI). For example, between 2010 and 2013 the pharmaceutical industry made the highest number of requests for EMA documents under the agency's reactive access policy (Bonini *et al*. 2014). There is also evidence that some individuals and institutions from outside the traditional regulatory network have the capacity to re-analyse CSRs and hence achieve at least some of EMA's goals such as identifying outcome reporting biases or scrutinising scientific committee decision-making (Maund *et al*. 2014). For example, a few medical researchers and health technology assessors have conducted studies using CSRs that were requested through FOI requests and other legal challenges (Vedula *et al*. 2013; Maund *et al*. 2014; Hodkinson *et al*. 2016).

On the other hand, far fewer medical researchers operating outside the regulatory network than might be assumed currently have the capacity to conduct high quality CSRs re-analyses. Although medical researchers are familiar with analysing summary level results in medical journals and trial registers, CSRs present a very different prospect. One of the most significant issues is that very few medical researchers have ever even heard of CSRs let alone re-analysed them. For example, even those who strongly demanded that EMA release CSRs without delay admit they are unfamiliar with them including Cochrane Collaboration reviewers (Doshi *et al*. 2013: 2; Doshi and Jefferson, 2013b). This may also partly explain why so few academic or research institutions requested access to CSRs or other documents between 2010 and 2013 through EMA's reactive access policy (Chapter VI) (Bonini *et al*. 2014). In the long-term, researchers may become more familiar with CSRs as they become increasingly publicly available and receivers become more sophisticated in analysing such large datasets (Doshi *et al*., 2013; Ebrahim *et al*. 2014). However, in the short term at least, there is unlikely to be the anticipated capacity from those outside the regulatory network to re-analyse CSRs that have traditionally been exclusively used by industry and the regulators. In turn, these capacity issues significantly weaken the effectiveness of the regulators' policy in achieving most of its goals.

(8.3.3) Conveying the results of re-analyses

Another advantage of EMA's CSRs policy for the medical community is that there are no restrictions on conducting re-analyses (EMA, 2014b). While EMA was developing its CSRs policy, the regulators debated placing requirements and safeguards to ensure re-analyses were high quality and underwent rigorous regulatory scrutiny (Eichler *et al*. 2012). This included establishing quality standards, establishing a system for regulatory action, requesting statistical analysis plans from prospective re-analysers, and establishing a "view on-screen only" document presentation mode (Eichler *et al*. 2012; EMA, 2013a; Norgine, 2013; EORTC, 2013; Torjesen, 2014). However, the agency's final policy placed no such safeguards on the quality of re-analyses or how results should be conveyed to the regulators and the public (EMA, 2014b). For those outside the regulatory network, this policy decision has the distinct advantage of reducing unnecessary burdens on those conducting re-analyses. In particular, some argued that any restrictions would have "watered down" the effectiveness of EMA's policy in enabling re-analyses (Torjesen, 2014). For example, EMA removed an original view on-screen only document presentation mode so that outsiders could "download, save, and print clinical data" (Bonini *et al*. 2014). EMA's CSRs policy also enables outsiders to freely re-analyse documents without first contacting the regulators, which can potentially reduce the burden on EMA (e.g. not having to review proposals). Therefore EMA's policy has the strength of enabling re-analyses of CSRs data without the involvement of the regulators thus potentially improving its effectiveness in achieving its overriding goal of enabling re-analyses. However, there are also important consequences of removing all restrictions on re-analyses for the achievement of EMA's ultimate goals.

One important issue is that removing all restrictions enables poor quality re-analyses to be conducted. In turn, this significantly weakens the effectiveness of EMA's policies in achieving all of its policy goals (Serptus, 2013; Mello *et al*. 2013; EORTC, 2014; IAPO, 2014; Greenacre, 2014; Institute of Medicine, 2015; FEAM[69], 2013). Poor quality re-analyses can occur when re-analysers misinterpret complicated CSRs data (Greenacre, 2014). There are many examples of when EMA regulators have experienced medical researchers conducting meta-analyses that were later found to be flawed and contradicted by future studies (Michele, 2010; EMA, 2011c; Krumholz and Ross, 2011; Eichler *et al*. 2012; BioIndustry Association, 2013; IAPA, 2013).

[69] Federation of European Academies of Medicines

'Independent' re-analysers can also have conflicts of interest that weaken the quality of their results (Ebrahim *et al*. 2014). For example, EMA regulators identify numerous reasons why those outside the regulatory network may be motivated to conduct poor quality analyses including "personal advancement in academia, confirmation of previously defended positions, or simply raising one's own visibility within the scientific community" (Eichler *et al*. 2012). By not introducing safeguards, poor quality analyses can reduce the effectiveness of EMA's policy in achieving any of its goals and have unwanted consequences (EFPIA, 2013; Institute of Medicine, 2015).

A second issue is that placing restrictions on re-analyses has resulted in more disputes over the benefits and risks of medicines (Löfstedt and Way, 2016b). CSRs are complicated documents and the results of re-analyses can be contested and debated with 'independent' medical researchers coming to conflicting conclusions. This can be most clearly seen when Cochrane Collaboration researchers re-analysed CSRs on Tamiflu. The results were immediately published on Cochrane's website and in the *British Medical Journal,* notably, without the involvement of the regulators (Cochrane Collaboration, 2014; Jefferson *et al*. 2014). The results subsequently received worldwide media coverage and were then strongly contested and debated in the public domain by numerous scientists (Muthuri *et al*. 2014; Kmietowicz, 2014; Butler, 2014). What is interesting is that these discussions took place in the public domain rather than behind closed doors at academic meetings (Löfstedt and Way, 2016b). Therefore EMA's policy has resulted in disputes over the regulators' interpretations of CSRs taking place in the public domain.

A third issue is that not placing restrictions on re-analyses has questioned the competence of decision-making in EMA's scientific committees. In contrast to summary level results reported in medical journals and trial registers, CSRs are the main source of information used by scientific committees to interpret the benefits and risks of medicines. This means that re-analyses with findings that question the benefit-risk balance of a medicine will indirectly be a criticism of the regulators' scientific committees' opinions and competence. Beyond Tamiflu, the results of many re-analyses were also directly used to question the competence of the regulators' decision-making process including studies on antidepressants, heart medications, de-worming treatments, and others (Butler, 2014; Ebrahim *et al*. 2014). There is also clear evidence that re-analyses that challenge the regulators' scientific opinions receive much greater

attention – and are much more likely to be published – than positive confirmatory analyses (*see* Ebrahim *et al*. 2014 for a discussion). Therefore EMA's policies has significantly increased the number of criticisms of scientific committee experts.

Taken together these three issues have important consequences for the effectiveness of EMA's CSRs policy. First, EMA's policy will continue to cause outsiders to question the competence of EMA's scientific committees, which could result in undermining trust in the regulatory approval system (Institute of Medicine, 2015; EuropaBio, 2013; EFPIA, 2013). In turn, there are concerns that this could cause significant unwanted effects of EMA's policy or as the Institute of Medicine (2015) puts it: "mistrust could ultimately lead to seriously flawed clinical care decisions, unwarranted patient concerns about the quality of care, or avoidable patient anxiety" (Institute of Medicine, 2015). Second, EMA's policy will continue to increase the need for the regulators to respond to invalid secondary re-analyses, which is an issue that others have found particularly difficult in the past (*see* Wallentin *et al*. 2014 for a discussion). Third, EMA's policy has resulted in patients and doctors receiving more (uncertain) information pointing to potential safety problems with their medicine. This raises important questions about EMA's role in ensuring that patients receive high quality information from re-analyses. As the International Alliance of Patient Organisations (IAPO, 2013: 96) comments: "So what are the patient and public (and even clinicians) to do in the case of contradictory or challenging findings based on a secondary analysis?". Therefore there are important consequences for the effectiveness of EMA's CSRs policy from not implementing a system of quality control and how the results of re-analyses are to be disseminated.

(8.4) Implications of survey findings

The overriding goal of EMA's input policies for patients and doctors is to better inform them about the benefits and risks of medicines evaluated by EMA's scientific committees. For EMA's CSRs policy, in particular, the case study evidence shows that patients and doctors are highly unlikely to become better informed by accessing trial registers or EMA's CSRs web-portal *directly* (Lang, 2013). Instead, they are much more likely to (potentially) gain a better understanding of the benefits and risks of EMA approved medicines *indirectly* from intermediaries re-packaging information and conveying the results of re-analyses (Chapter VI).

In order to understand the effectiveness of EMA's policies in achieving its goals for patients and doctors, five main findings from the surveys are discussed.

(8.4.1) Patients and doctors want more and better quality information

One implication of the survey findings is that many patients and doctors agree with the main goals of EMA's input policies of providing more information to improve decision-making (Chapter VI) (EMA, 2014b, 2015a; 2016a). One finding was that patients and, to a lesser extent, doctors desire more information on medicines. Almost 40% of patients said that there is too little information on medicines currently publicly available (Table 7.2). While significantly fewer doctors felt the same, almost a third still indicated that they feel there is too little information available. The large majority of patients and just over 50% of doctors also agreed that patients receiving more information on the safety of medicines would increase their medicine-taking confidence (Table 7.1)[70].

A second implication of the surveys is that providing patients and doctors with a better understanding of the benefits and risks of medicines is also a highly desirable and appropriate goal for EMA's input policies. A second key survey finding was that large numbers of patients and especially doctors believe that medicines information currently publicly available is of poor quality and communicated ineffectively. The large majority of patients and even more doctors felt that the health information they receive is affected by politics, sensationalised by the media, and generally biased (Figure 7.1). Over 40% of doctors also felt that health information facts are not communicated properly, are not easy to understand by the general public, and are generally not clear (Figure 7.3). Although patients were less negative about the quality of information and how it is communicated, over a quarter of patients also shared these views.

Taken together these findings have direct implications for EMA's policy decision not to place safeguards on outsiders conducting re-analyses (EMA, 2014b). In particular, along with ensuring that re-analyses conducted outside the regulatory network are highly accurate, the

[70] This should not be misinterpreted as showing that respondents' confidence would necessarily increase after receiving 'more' information. Rather, that the majority of doctors and patients agree that more information in general would be *expected* to increase patients' confidence in taking medicines.

regulators will have to ensure that patients receive better quality and well communicated information from re-analyses. This is important because as, the European Organisation for Research and Treatment of Cancer (EORTC) comments: "Incorrect analysis and interpretation of results could result in considerable damage to public health [and] this damage could be irreversible" (EORTC: 89: 1-2). In other words, EMA needs to respond proactively to re-analyses that are being disputed in the public domain. This will also present a challenging task for the regulators because poor quality or poorly communicated re-analyses of CSRs could further damage an already vulnerable pharmaceutical information and communication environment. For example, the Institute of Medicine (2015) make clear that the regulators may find it difficult to refute spurious claims publicised in the media even if they are later disapproved in other published articles.

(8.4.2) Patient and doctors are confused about the contribution of the regulators

Another main survey finding was that many patients and even doctors have not heard of the authorities that regulate medicines. While over three quarters of patients and 20% of doctors indicated that they had not even heard of EMA, 56% of patients and 6% of doctors said the same about their relevant NCA. These figures are also likely to be higher as this is a self-reported awareness question that is susceptible to social desirability bias (Fisher, 1993). Further, when comparing these findings with other surveys, EMA and, to a lesser extent, NCAs can also be seen to be much less well known than comparable agencies such as the US FDA and EFSA (EFSA, 2010; Löfstedt *et al*. 2011). For example, the results of a 2011 survey showed that 98% of US public respondents (N=1,000) had at least heard of the FDA. This lack of visibility in the channels of information also does not deviate fundamentally from earlier general public survey findings (Bouder *et al*., 2015).

Several further questions also showed that, even if some patients and doctors have heard of the institutions that regulate pharmaceuticals, the large majority are confused about their contribution to the pharmaceutical system. First, the large majority of patients and doctors are unaware of the regulators' medicines, health alerts, or other health communication activities. This means that most patients and doctors are unaware of the benefit-risk communication activities of both their national and supranational EU regulatory authorities. Second, over three

quarters claimed not to have a good knowledge of how EMA and their NCA assess the safety of medicines[71].

The findings that patients and doctors are confused about the contribution of regulatory authorities to the pharmaceutical system has important implications. First, the findings provide further evidence that patients and doctors are highly unlikely to read CSRs directly by going online and accessing EMA's CSRs web-portal (Lang, 2013; Drug Commission of the German Medical Association, 2013). For example, as the Drug Commission of the German Medical Association comment:

> *"Performing a proper re-analysis on the basis of raw data will need much expertise, high skills and technical equipment usually not available to interested clinicians"*

Although the results do not directly examine comprehension (e.g. whether patients do actually understand information in EMA documents), it seems very unlikely that patients and doctors will become more informed about an institution simply by receiving documents used by the agency that are so unfamiliar and which operates in such a technical field (e.g. documents used by experts working in EMA's scientific committees to evaluate the safety and efficacy of medicines) (Lang, 2013). Second, the findings raise important questions about EMA's ability to respond to the results of CSRs re-analyses whether they are positive or negative. Although the regulators see themselves as key providers of safety information (EMA, 2014g), refuting the results of poor quality analyses will be especially difficult if patients and the public are unaware of who the regulators are (*see* Tuler and Kasperson, 2014; Siegrist *et al*. 2007; Kasperson *et al*. 2014). Therefore this is one notable issue that needs to be addressed if the regulators' transparency goals are to be achieved for patients and doctors.

(8.4.3) Patients and doctors disagree over when re-analysed data should be conveyed

The fourth main finding from the surveys was that doctors and patients disagree over when newly found information pointing to a safety issue should be conveyed to the public. While the

[71] To be clear, rather than measuring whether respondents do, indeed, have good knowledge of how the regulators assess the safety of medicines, the self-reported nature of this question points to respondents' confidence in their knowledge of how the regulators' assesses the safety of medicines. This means that most patients and doctors either have low knowledge of how medicines are evaluated or, at least, have low confidence in their knowledge of how medicines are evaluated.

majority of patients (60%) think it is a good idea to inform the general public about a possible safety issue before a scientific analysis has been conducted, the majority of doctors (76%) think doing so would be a bad idea. In agreement with this finding, over half of patients surveyed also indicated that they would prefer to receive safety information when there is a possible sign of a safety problem (i.e. as soon as it is available) and before it has been investigated at all and before either industry or the regulators believe the issue is related to the medicine. In sharp contrast to the views of patients, less than a quarter of doctors indicated the same. Instead, over 60% of doctors indicated that either industry or the regulators should investigate the possible safety issue first and that information should only be conveyed when they believe that the problem is related to the medicine.

These results have important implications for EMA's decision not to review the results of re-analyses before they are made public. First, the majority of patients are likely to agree with EMA that the results of CSRs re-analyses should be conveyed to the public before first being investigated by the regulators or industry (i.e. to confirm their findings). They are also likely to agree with EMA that external researchers should not have to discuss their findings with the regulators before publishing their results. Rather, the results should be conveyed to the public when re-analysers identify a possible sign of a safety problem.

In sharp contrast to patients, the majority of doctors are likely to strongly disagree with the regulators' decision. This is not a surprising finding. For example, a February 2015 British Medical Association (BMA) study of 15,560 UK GPs found that 37% think their workload is unmanageable (BMA, 2015). If more unsubstantiated medicines data is released without being investigated by industry or the regulators then doctors will arguably be the ones taking on the burden of dealing with concerned patients. This is also most likely why the two most popular open ended responses for doctors regarding the best way to communicate medicines information were (1) information should be conveyed face-to-face with doctors and (2) healthcare professionals and information should be communicated simply and in a comprehensible way (Table 7.3). Thus once doctors become aware of EMA's CSRs policy they are highly likely to question the reasoning for it (Löfstedt *et al*. 2015).

(7.4.4) Patients will have varying reactions to re-analysed data

One of the most important findings from the surveys was that patients are likely to have varying reactions to receiving the results of CSRs re-analyses that point to safety problems with their medicines. The majority of patients (56%) indicated that they would 'seek additional advice about the medicine'. Although this result does not show whether patients would actually seek additional advice, it shows their perceived likelihood of doing so (i.e. behavioural intentions). On the one hand, it is highly promising that the majority of patients would 'seek additional advice' when receiving uncertain information on their medicines. For example, this behaviour is what would be recommended by the regulators and healthcare professionals in such a scenario with NHS Choices (2015), the official health website of the UK National Health Service, making clear that patients should "…only ever stop taking prescribed medication if your GP specifically advises you to". This advice is also especially relevant considering the sample was of individuals with serious long-term medical conditions. One consequence of this finding is that the impact of poor quality re-analyses of CSRs on prescription compliance is likely to be much weaker for these groups assuming they sought advice from sources that were aware that the re-analyses were of poor quality (e.g. doctors or pharmacists). On the other hand, the capacity may not exist to attend to patients seeking additional advice over the safety of medicines after the results of re-analyses have been disseminated. Therefore the high quantity of information seekers suggests that doctors are likely to see an increase of patients when the results of both high and low quality CSRs re-analyses are communicated to the public via intermediaries. In particular, the majority of patients are most likely to obtain such additional information from their pharmacist, or their doctor as these were rated as two of the easiest and most trustworthy sources for patients to obtain medicines information. As discussed in the previous section, this could cause concern for healthcare professionals as many are already overworked and overloaded with patients.

An arguably more significant issue is the finding that, although many would seek additional advice, a large numbers of patients would either stop (26%) or reduce (9%) the dose of their medicine. One key implication of these results is that, in the event that the results of CSRs re-analyses identify a possible safety issue with a medicine, then a large downfall of prescription compliance can be expected. For example, it took only one article (Nissen and Wolski, 2007) published in the New England Journal of Medicine and four months for 60% of patients taking

Avandia (roglitazone)—a type II diabetes drug—to discontinue their medication based on incomplete information (Saul, 2007; Löfstedt, 2010).

Furthermore, the likelihood of patients indicating one of these two options also varied significantly depending on their medical condition and, moreover, their country and geographic region. For example, when combining these response categories (country and medical condition), 68% of respondents from Germany diagnosed with IPF compared to 11% of UK respondents diagnosed with HIV/AIDS said they would more likely 'stop taking' or 'reduce the dose' of their medicine (Figure 4). Confirming the results from a general public survey (Bouder *et al*. 2015), patients from Germany, Spain, and France were also significantly more likely to stop taking their medicine than respondents from the UK. The surveys also show that a prescription non-compliance response is also likely to vary between medical conditions and nations. With that said, even patients with HIV/AIDS taking antiretroviral treatments can be expected to stop taking their medicines if they receive information on a possible safety issue from re-analysed CSRs with almost 30% of patients from Germany indicating they would either stop taking their medicine or reduce the dose. It is therefore clear that EMA will have to work closely with national authorities and patient groups that have intimate localised knowledge of national healthcare systems and patient communities. This includes an in-depth understanding of the actor groups that are at the coal-face of communicating benefit-risk information with the public and, as this study shows, who are crucial for maintaining public trust in the pharmaceutical system. In so doing, one goal will be to improve doctors' understanding of the benefit-risk evaluation system.

Chapter IX: CONCLUSION AND RECOMMENDATIONS

This thesis explored and critically examined the concept of transparency in risk regulation in-depth. The first main contribution of the study is the creation of an original typology (Chapter II). The typology crucially enabled the investigator to disambiguate the concept of transparency in risk regulation and create clear distinctions between different policies (Chapter II) (Heald, 2006; Meijer *et al*. 2015). Such distinctions were made between what risk regulators seek to make more transparent (objects), how (mechanisms), why (goals), and for whom (audiences) (Gupta and Mason, 2014). The typology can now be used by future researchers seeking to navigate the seriously fragmented transparency literature (Chapter III). For example, in this study the typology enabled the investigator to identify that, although there have been numerous studies examining the effectiveness of *output* transparency policies (Arvai and Rivers III, 2014; Way *et al*. 2017), much more empirical evidence on the effectiveness of *input* transparency policies was, and still is, needed (Etzioni, 2010; Löfstedt, 2013). The typology can also be used by future researchers measuring and evaluating transparency policy effectiveness. For example, in this study the typology enabled the investigator to identify significant changes to EMA's transparency strategy over time including the remarkable evolution of input type policies (Chapters V-VIII).

The second main contribution of this thesis is that it provides much needed empirical evidence on the effectiveness of transparency in risk regulation. In particular, the EMA case study generated in-depth evidence on the effectiveness of various input transparency policies in achieving the agency's public policy objectives. The case study narrative in itself provides a significant contribution to the literature (Chapter VIII). Yet, one of the most important overriding outcomes was that regulatory authorities should not assume that introducing policies designed to enhance transparency will necessarily achieve their expected goals. Rather, transparency policies need to be measured and evaluated for their effectiveness in the achievement of specific and attainable objectives (Coglianese, 2012; Heald, 2012). While the case study identified many important arguments for transparency (Chapter VI), it also found many reasons why some policies will be more (or less) effective than others (Chapter VIII).

(9.1) Captivated by full disclosure

One of the most important issues that significantly weakened the effectiveness of EMA's transparency strategy centred on the quantity of transparency. In particular, the EMA case study showed that over time the regulators became more and more captivated with publishing increasingly large quantities of input data online (Chapter VIII). There is evidence that the regulators felt they had little choice (personal communication, 2013) and the extent of the external pressure put on EMA should not be underestimated. For example, the regulators received criticisms from a multiplicity of different stakeholders and actors ranging from medical researchers wishing to re-analyse industry data (Gøtzsche and Jørgensen, 2011; Doshi *et al*. 2013) to a succession of European ombudsmen (Ombudsman, 2010; O'Reilly, 2013, 2014), and several MEP politicians (Willmott, 2013) (Chapters V and VI). Yet, the in-depth case study also identified many reasons why becoming captivated by the quantity of transparency can significantly weaken the effectiveness of different policies. This is particularly important because many other regulatory authorities have taken or are debating taking a similar approach to EMA (Url, 2014; FDA, 2014). For example, since 2014 EFSA has begun providing a "treasure trove" of food safety input data from its "data warehouse" (Url, 2014).

One important issue with being captivated by the quantity of transparency is that there are many reasons why *full* input disclosure may not be feasible or desirable (Birchall, 2011; Gupta and Mason, 2014). Although some have argued that industry have been overly defensive (e.g. Eichler *et al.* 2013), there are still significant unresolved commercial confidentiality and privacy issues that limit the quantity of information that can feasibly or desirably be made publicly available (*see* Price II and Minssen, 2015 for a discussion). Publishing large quantities of input data has also resulted in substantially increasing legal action against EMA (EMA, 2013, 2015). Second, the assumption that all documents and information can simply be uploaded online with the click of a mouse is naïve. There are complicated challenges with anonymising data, creating online systems for sharing data, and tackling non-compliance. Therefore full input disclosure is not necessarily feasible or desirable, which raises questions over when transparency in risk regulation is satisfied (Hood, 2001).

A second main issue with being captivated by the quantity of transparency is that the capacity and infrastructures needed to achieve the regulator's goals may not yet exist. A key assumption with introducing any new transparency policy is that outsiders can understand the information made available and have the capacity and resources needed to achieve the regulator's second order goals (Roberts, 2006; Gupta, 2008). As Mitchell (2011) argues: "complex infrastructures of monitoring and verification are needed to render disclosed information usable". Yet, the EMA case showed that many of the audiences of transparency are highly unlikely to be able to use much of the information being made available (Chapter VIII). While there are significant issues with trial registration and results reporting (EMA, 2013, 2014; Viergever and Li, 2015; Chen *et al*. 2016), those demanding EMA provide access to CSRs openly admit that most medical researchers have never heard of the documents (Doshi *et al*. 2013). This seriously questions whether full disclosure will actually enhance transparency if the information made available is not comprehensible or actionable (Gupta and Mason, 2014). It also seriously questions how intermediaries will repackage and convey their own interpretations (O Neill, 2006; Mason and O'Neill, 2008). For example, the EMA case showed that publishing large quantities of data has resulted in more poor quality re-analyses being conducted, more disputes over what the transparent data means, and more criticisms of the regulator's competence in interpreting data (Chapter VIII). This means that there are important issues with full disclosure that centre on the capacity of outsiders to interpret and use the data made available and, in turn, convey key findings as intermediaries (O'Neill, 2006).

A third main issue with being captivated by the quantity of transparency is that the regulators have inadvertently ignored the importance of communication. Information made publically available has to be interpreted for meaning and in the context of medicines this requires expert understanding and communication (Fischhoff *et al.* 2011; Fischhoff, 2013). If transparency policies are not accompanied by effective (benefit-risk) communication, then they are unlikely to achieve the regulator's goals (Löfstedt and Bouder, 2014). For example, O'Neill and Mason (2008) comment:

> *"Complete transparency might entail such detailed and complex discussion of the scientific process by which conclusions were reached as to obscure the major points of an argument made to non-expert audiences or to weaken the policy relevance and vividness of the communication".*

This means that the rise of input transparency policies presents a new challenge for transparency and risk communication scholars especially with regard to addressing the tension between the accessibility and comprehensibility of information made publicly available (Hood, 2007; Meijer, 2016). While there is a need for transparency policies to be accompanied by state-of-the-art risk communication science (Löfstedt and Bouder, 2014), there is equally a need for the sub-field of risk communication to engage with the challenges presented by transparency (*see* section 9.2) (Meijer, 2016).

A fourth main issue with being captivated by the quantity of transparency is that full disclosure is resource intensive. The EMA case study showed many ways that seeking to enhance transparency can consume substantial resources (Chapter VI). This includes EMA responding to external re-analyses of CSRs, anonymising and redacting millions of pages of regulatory documents, dealing with legal action against the agency, and developing and managing information systems for making data publicly available, as well as many other resource intensive activities (Chapter VIII). For example, in September 2013 EMA established "a dedicated multidisciplinary team of 13 full-time equivalent staff members working every day on access to documents and requests for documents" (Pott, 2015).

One important issue with consuming so many resources is that the agency will be less able to respond to the new more open information environment. For example, EMA will be less able to respond to the results of both high and poor quality re-analyses of regulatory data that challenge the benefit-risk profile of medicines authorised through EMA's centralised procedure. A second key issue is that focusing on full disclosure will mean that EMA will have fewer resources to put towards other policies that may be more effective in achieving their ultimate public policy objectives (Meijer *et al*. 2015). For example, the large resource consumption of EMA's CSRs policy means that the agency will have fewer resources to improve trial registration and results reporting, which are two policies that many have argued will be much more effective in achieving the regulators' ultimate goal of minimising non-publication and associated biases (Science and Technology Committee, 2013; Hoffmann *et al*. 2017). Therefore full disclosure policies are unlikely to be the most effective way of achieving the regulator's goals as they can draw resources away from other potentially more useful policies (Meijer *et al*. 2015).

(9.2) Re-conceptualising transparency as a communication process

The results of this study have important implications for how transparency has been conceptualised in the academic literature and policymaking. Transparency is widely understood by most scholars to mean more than just access to documents (Birkinshaw, 2006). Several academics and policymakers also make clear that the concept extends beyond 'openness' to "embrace simplicity and comprehensibility" (*see* Alemanno, 2014 for a discussion; Heald, 2006, 2015; Meijer *et al*. 2012; Baume and Popodoupolos, 2015). As Heald (2006: 26) explains:

> *"...it is possible for an organisation to be open about its documents and procedures but yet not be transparent to relevant audiences if the information is perceived as incoherent. Openness might therefore be thought of as a characteristic of an organisation, whereas transparency also requires external receptors capable of processing the information made available".*[72]

Therefore a central tenet underpinning contemporary transparency theory is that data/information needs to be comprehensible and understandable in order to be processed by 'outsiders' (i.e. the audiences of the regulator's policies). This has also been emphasised by some policymakers and many academics (Coglianese, 2009; Alemanno, 2014). When defining transparency, Robert Soderman, the first European ombudsman, emphasised that "the process through which public authorities make decisions should be *understandable* and open" [italics added for emphasis] (Curtin and Meijer, 2006: 110). Patrick Birkinshaw (2006) highlighted the importance of comprehensibility and simplicity when noting that "complexity and disorder" are an "obstacle" to transparency. What this means is that in order to enhance transparency, rather than simply become more open or provide access to documents (e.g. as a legal requirement), organisations need to ensure that data/information is *comprehensible* and hence can be received, digested, processed and used by target audiences (Heald, 2006; Gupta and Mason, 2014).

However, this study shows that these dominant conceptualisations of transparency do not go far enough. What has been largely omitted from contemporary transparency theory is the

[72] Heald (2015: 3) also clarifies: "If there is to be a distinction, openness might be seen as pertaining to the 'watched' (e.g. information is made available) whereas transparency also requires the watcher to be able to process that information".

paramount importance of actually *communicating* the data/information made publicly available by regulatory authorities. If information is not communicated then it is unlikely to be comprehensible or understood by any audience (Tsoukas, 1997; Fenster, 2006; Keohane *et al*. 2014). Emphasising communication may seem trivial. Yet, there is clear evidence from this thesis that EMA regulators and many transparency scholars have inadvertently ignored the importance and complexity of communicating information. For example, the EMA case study showed that the regulators became captivated by increasing the quantity of data/information made publicly available (e.g. the number of pages uploaded) (section 9.1). In turn, they paid insufficient attention to how that data/information is received, understood, and used by external receptors (Chapter VIII). This crucial issue is concisely explained by O'Neill (2006):

> *"An emphasis on transparency encourages us to think of information as detachable from communication, and of information as a process of 'transferring' content, rather than as achieved only by speech-acts that communicate with specific audiences. […]. [By conceptualizing transparency in this way] …it then becomes natural to see informing mainly as a matter of disclosure and/or dissemination by those in control of information, and to overlook or downplay the fact that effective communication must reach audiences".*

Effective transparency requires effective (benefit-risk) communication and if communication is not integrated with transparency theories then data/information will continue to be 'hidden in plain sight' (Fischhoff, 2013).

Following this line of argumentation, it is strongly argued in this thesis that transparency in risk regulation needs to be re-conceptualised as a risk communication process. Although a handful of others have discussed the intersection between transparency and communication (O' Neill, 2006; Fenster, 2006; Keohane *et al*. 2014; Bouder *et al*. 2015; Way and Lofstedt, 2016a, 2016b; Meijer, 2016), this thesis provides concrete evidence on why integrating communication and contemporary transparency theory is so important. In particular, the EMA case showed that transparency is unlikely to be effective and the regulator's goals unlikely to be achieved if policies focus on simply providing greater access to raw data while not recognising the importance of communicating information made publicly available to relevant audiences (Chapter VIII). To be clear, while most researchers have focused on simply connecting transparency with comprehensibility, this thesis argues that there needs to be a much more explicit engagement with the process of communicating data/information effectively with different audiences.

(9.3) Implications and recommendations

Reconceptualising transparency as a communication process subsequently has important implications for risk research and especially the sub-field of risk communication. One main implication is that the risk communication literature can be usefully applied to understanding the effectiveness of many existing transparency policies. While several transparency scholars have lamented the lack of empirical research on transparency (e.g. Etzioni, 2010), others have argued that since 2010 there has been a noticeable growth of empirical research primarily in the form of policy experiments (Cucciniello *et al*. 2017). Yet, when transparency is reconceptualised as a risk communication process, over 50 years of theoretical and empirical research can be directly applied to understanding the effectiveness of different regulatory policies. For example, when reviewing the literature on transparency in risk regulation, this thesis found that output and process transparency policies especially have been long debated in the risk communication literature (Chapter III). Therefore many transparency policies can be improved by drawing on the collective wealth of scientific risk communication research (Slovic, 2000; Fischhoff *et al*. 2011; Fischhoff, 2013; Arvai and Rivers III, 2014; National Academy of Science, 2016; Jamieson *et al.* 2017).

A second main implication of reconceptualising transparency as a risk communication process is that risk communication scholars can significantly contribute to improving transparency policy effectiveness. The case study identified two areas where the sub-field of risk communication could make the most significant impact. First, the EMA case highlighted the importance of intermediaries in assessing/analysing data and then communicating new findings. Risk communication scholars could play a central role in investigating and improving how these new intermediaries communicate findings from publicly available data (Mitchell, 2011; Dunwoody and Griffin, 2014). They could examine how effective intermediaries are in achieving the ultimate risk communication goals that underpin most transparency policies (Brewer, 2011). Risk communication scholars could also analyse the impact of transparency on increasing the amount of uncertainty over scientific findings that is available in the public domain (e.g. public debates over Tamiflu or human papilloma virus vaccines) (Lofstedt and Bouder, 2017). For example, the social amplification of risk framework could inform new studies investigating the impact of the regulator's policies on public understanding of risk, benefit-risk information and medical science (Kasperson *et al.* 1988; Pidgeon, 2003).

Second, the EMA case found that transparency policies have profoundly changed the risk communication environment. This has led to new, previously unexamined, risk communication challenges for regulatory agencies. For example, making the data that underpins decision-making in EMA's scientific committees publicly available was found to substantially increase public scrutiny of the regulators and led to indirect challenges of their competence (Chapter VIII). Regardless of whether these re-analyses or criticisms have been beneficial, accurate or fair, enabling external scrutiny presents a major new risk communication challenge for practitioners. For example, how should the regulators respond to growing challenges to their competence? How should government authorities and scientists respond when there may be little time to check the quality of external re-analyses? By re-conceptualising transparency as a risk communication process, scholars can examine the new regulatory environment and help tackle the most pressing transparency challenges affecting practitioners.

A third main implication of re-conceptualising transparency as a risk communication process is that risk communication scholars and practitioners can work more closely together on improving policy effectiveness. On the one hand, this will mean that researchers will have to ensure that new findings are applicable to the new challenges affecting regulatory authorities. Indeed, increasing the policy relevance of risk communication research can be a significant issue or as Fischhoff *et al*. (2011: 2) put it:

> *"...academic researchers' theoretical interests often lead to studying communication processes in isolation, leaving gaps as to how research results apply to complex, real-world situations. Unable to access the research literature, practitioners rely on their intuition, unproven best practices, and popular accounts of psychological research."*

In order to improve the relevance of risk communication research, academics will need to more proactively engage with the new more transparent risk communication environment. In so doing, there is an important role for academics to make evidence-based recommendations that are suited to the rapidly changing and more transparent risk communication environment.

On the other hand, there is equally a need for regulatory authorities to provide meaningful opportunities for scholars to contribute. This presents a major challenge as transparency is often discussed at a level of abstraction that obscures the crucial connection between comprehensibility and communication. Furthermore, there was clear evidence from the case study that the regulators have increasingly divided the concepts of transparency and risk

communication over time. For example, while EMA emphasised the importance of communication in the development of its transparency strategy in 2005 (EMA, 2005b), the agency had all but removed 'communication' from its transparency policies by 2013 (Chapter VIII). Some interviewees described this as a 'silo-ing' effect where transparency and communication have been increasingly separated within the organisation (personal communication, 2014). Thus connecting transparency with (risk) communication will be a major challenge for regulatory authorities and improving transparency policy effectiveness.

Taken together, these key issues highlight the need to measure and evaluate the effectiveness of transparency in risk regulation and not just in the pharmaceutical domain. In seeking to identify and implement the most effective transparency policies, fives concrete recommendations are provided.

(9.3.1) Establish an independent benefit-risk communication advisory board at EMA

EMA should establish an independent Benefit-Risk Communication Advisory Board (Bouder, 2011; Bouder *et al*. 2015). As suggested by the investigator and colleagues (Bouder *et al*. 2015), the board can be modelled on the FDA's highly successful Risk Communication Advisory Committee (RCAC, 2017). The board should not be a new EMA committee such as PRAC or CHMP. Rather, it should be comprised of experts from the sub-field of risk communication and the medical community. The main purpose of the board would be to provide support for EMA in a new more transparent risk communication environment. For example, the FDA's RCAC has addressed topics such as recent developments in the risk communication literature, the challenges of communicating more effectively with healthcare professionals, how to improve agency message designs, and many others (Fischhoff et al. 2011; FDA, 2016). The first objective of EMA's board could be to review the evidence on the effectiveness of the agency's transparency policies and its risk communication strategies. For example, the board could first conduct a review on the state-of-the-art risk communication science (Fischhoff *et al*. 2011) and the findings of this 4-year case study.

(9.3.2) Build relationships with trusted intermediaries

The second recommendation is that EMA should build closer relationships with trusted intermediaries. EMA's policies have resulted in enormous quantities of input data and information being published online. There is clear evidence that re-analysers will convey their findings to patients and doctors via intermediaries without first consulting the regulators (Jefferson *et al*. 2014; Butler 2014; Ebrahim *et al*. 2014). This means that intermediaries will have a new role in communicating benefit-risk information to the public. As several senior EMA regulators make clear: "the media play a key role and need to provide accurate information gleaned from documents they receive from EMA" (Bonini *et al*. 2014). Yet, EMA cannot assume that intermediaries including the media and others will be effective in communicating benefit-risk information (Kasperson *et al*. 1988; Pidgeon *et al*. 2003; Barnett and Breakwell, 2003). Rather, EMA need to build relationships with trusted intermediaries so that they are more prepared to respond to the results of re-analyses. For example, the regulators can establish trusted networks with patients and doctor groups and key news media outlets. Building trusted relationships can also help to ensure that the regulators can respond quickly and effectively to the results of both high and low quality re-analyses of clinical trial data. This is particularly important because EMA does not have the capacity or resources to ensure that the results of all re-analyses are communicated effectively by itself. This is especially true with the new resource-intensive demands of the UK exiting the EU and the agency most likely being forced to move its headquarters out of London (Wilsdon, 2017).

(9.3.3) A conference on evidence-based transparency

The third recommendation is that a conference on evidence based transparency should be held at the European Commission (Bouder *et al*. 2015). The ambiguity of transparency in risk regulation and the tendency for regulatory to become captivated by full disclosure emphasize the need to improve the regulator's transparency strategies. Policymakers often declare that transparency is important and needed. Yet, there is still little understanding of what needs to be made transparent, how, why and for whom, as well as the desired quantity and quality of transparency (Gupta and Mason *et al*. 2014). A conference could bring together both regulators and academics so that the latest evidence can be conveyed on which transparency policies work best, for whom, and why. Moreover, while historically there have been few critical

examinations of transparency in risk regulation (Etzioni, 2010; Löfstedt, 2013), recent findings show that more theoretical and empirical research is beginning to be conducted (Cucciniello *et al*. 2017). This means that there is much that has been learnt in recent years that could significantly benefit the regulators' strategies.

(9.3.4) Conduct more empirical research on effectiveness

One of the main findings from the literature review was that few real-world empirical studies have been conducted on transparency in risk regulation. While there is evidence of more research being completed (Cucciniello *et al*. 2017), there is still a great need to conduct more. Two main research avenues could be prioritised (also *see* O'Connor, 2016). First, the results of the EMA case study need to be compared with those of other regulatory organisations responsible for human health and the environment (e.g. EFSA, ECHA, FDA, Health Canada). Although EMA was considered a "typical" case (Chapter V), additional studies can investigate how EMA's policies and experiences compare with others. Second, there is a need to conduct more studies on the effectiveness of input and process transparency policies (Heald, 2006). While output transparency policies have received a great deal of attention in the fragmented literature, there remains only a handful of studies examining the effectiveness of other types of transparency (*see* Chapter, III for a discussion). Transparency promises a great deal. Yet, if the effectiveness of polices designed to enhance transparency are not measured and evaluated and key findings are not disseminated then they will never achieve their potential.

(9.3.5) A call for proposals from risk researchers

There is a real need for the risk research community and especially risk communication scholars to explore how transparency policies can become more effective. Although some have pointed to a connection between transparency and communication, this thesis clearly shows a fundamental and problematic disconnect between transparency and risk communication in the literature and policymaking. This disconnect needs to be reconciled and there is a wealth of expertise that would significantly benefit the development of effective policies (section 9.2). In order to reconcile this disconnect, this thesis calls for proposals exploring and examining the many ways that transparency connects and interacts with risk communication both theoretically and practically. By re-conceptualising transparency as a risk communication

process and with the evidence-based support of risk researchers, government regulatory authorities can work towards developing policies that are truly effective in enhancing transparency.

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Appendix A: Geographic regions of patient and doctor samples

Great Britain (%)			France (%)			Spain (%)			Germany (%)		
Region	*Patients*	*Doctors*	**Region**	*Patients*	*Doctors*	**Region**	*Patients*	*Doctors*	**Region**	*Patients*	*Doctors*
North & Yorkshire	13	12	**Paris region**	22	23	**North West and North East**	32	37	**Nielsen I (Hamburg, Bremen, Schleswig-Holstein, Lower Saxony)**	34	18
North West	14	10	**North West**	20	18	**Madrid and Central**	33	27	**Nielsen II (North Rhine Westphalia)**	12	14
Midlands	13	15	**North East**	19	17	**East**	15	19	**Nielsen III (a&b) (Hesse, Rhineland-Palatine, Saarland)**	23	34
South West & Wales	11	15	**South West**	19	15	**South and Canaries**	20	18	**Nielsen IV (Baden-Wuerttemberg)**	15	20
South East & Anglia	22	20	**South East**	20	26				**Nielsen V (a&b) (Barvaria)**	7	4
London	19	19							**Nielsen VI (Berlin, Mecklenburg-Western Pomerania)**	2	4
Scotland	7	8							**Nielsen VII (Thuringia)**	6	6
Northern Ireland	1	2									

Appendix B: Patient Questionnaire

PATIENT SCREENER

Thank you for your interest in participating in our study about health issues.

Your answers to our questions will be kept confidential, and will not be associated with your identity. Only group results will be reported.

You do not have to answer any questions you do not want to, and you can stop answering questions and end the survey at any time. If you choose to end the survey before completion, your answers will then be destroyed.

In determining whether you are an appropriate candidate for this survey, please answer the following questions.

PS1. In what year were you born?

_____ (*Year of birth*)

(IF 1996 OR HIGHER: TERMINATE)

PS 2. Please indicate whether you have been diagnosed with any of the following conditions. (For the purposes of this questionnaire, please select one answer only)

	(ALPHABETISED LIST)
1	HIV/AIDS
2	Idiopathic pulmonary fibrosis (IPF)
3	Multiple Sclerosis
4	Osteoporosis
5	Rheumatoid arthritis
6	Other

[If ONLY 'OTHER' SELECTED: TERMINATE]

PS 3. How long have you been diagnosed with this condition?

1. Less than a year
2. 1-2 years
3. 2-5 years
4. 5-10 years
5. 10 + years

[If 'LESS THAN A YEAR': TERMINATE]

PATIENT SCREENER CONTINUED

Please read the following five points carefully before agreeing to participate in this research.

- The aim of this research is to gain your views for academic research and improving healthcare communication only and is not intended to be promotional.
- The identity of respondents is confidential and none of your details will be passed on to any 3rd party.
- Any information you disclose will be treated in the strictest confidence and the results of the research aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to you as an individual.
- You have the right to withdraw from the survey at any time and to withhold information as you see fit.
- This survey is supported by a pharmaceutical company.

By proceeding to the next page, please confirm that you have read and understood the points above and are happy to proceed with the market research survey on this basis

(Please put a cross in the box)

TERMINATE TEXT: We're sorry, but you are not eligible to participate in this study. We appreciate your interest and hope that you will participate in future studies. Thank you!!

GENERAL COMMUNICATION OF HEALTH INFORAMTION

The remainder of the survey will take approximately 15 minutes to complete. Just as a reminder, you can stop answering questions and end this survey at any time.

We would first like to ask you some general questions about the communication of health information

Q1. Overall, do you feel that information about medicines and health alerts on issues such as H1-N1/swine flu, food recalls, etc. are communicated to the general public effectively?

1. Yes
2. No

Q2. Would you say that the amount of information about medicines currently publicly available is too much, the appropriate amount, or too little?

1. Too Much
2. Appropriate amount
3. Too Little

Q3. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding **the communication** of information about medicines and health information? *(Select one per row)*

	Agree Strongly	Agree Somewhat	Neither Agree Nor Disagree	Disagree Somewhat	Disagree Strongly	Don't Know
(RANDOMISE)						
1. There is a health information communication process in place to communicate with the general public effectively						
2. Health information is readily available						
3. There are several sources for health information						
4. Health information communicated to the general public is easy to understand						

Q4. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding **information** about medicines and health information? *(Select one per row)*

	Agree Strongly	Agree Somewhat	Neither Agree Nor Disagree	Disagree Somewhat	Disagree Strongly	Don't Know
(RANDOMISE]						

1.Politics affects what health information is communicated to the general public
2.Health information for the general public is generally unbiased
3.Health information facts are communicated properly
4.Health communications generally have consistent information
5.Health communications are generally clear
6.I trust health information from pharmaceutical companies
7.I trust health information from medicines regulators
8.Mainstream media sensationalizes health information

Q5(a). How easy is it for you to obtain information about medicines from each of the following sources?

Very Easy	Somewhat Easy	Neither Easy Nor Difficult	Somewhat Difficult	Very Difficult	Don't Know

(RANDOMISE)
1.Doctors
2.Local hospital
3.Internet in general
4.Media (e.g. newspapers, television, radio, etc.)
5.A medically qualified friend or relative
6.Patient advocacy groups
7.Pharmacy
8.Nurses
9.[Insert NCA – TBC]
10. EMA - European Medicines Agency
11. Medical Journals
12. Politicians
13. Pharmaceutical companies (including their websites)
14. Another friend or relative (not medically qualified)
15. Social media (e.g. twitter, Facebook)

Q5(b). How trustworthy do you believe the following sources are in providing you with advice on the side effects associated with specific medicines?

Very Trustworthy	Fairly Trustworthy	Neither Trustworthy Nor Untrustworthy	Not Very Trustworthy	Not at all trustworthy	Don't Know

(RANDOMISE)
1.Doctors
2.Local hospital
3.Internet in general
4.Media (e.g. newspapers, television, radio, etc.)
5.A medically qualified friend or relative

6.Patient advocacy groups
7.Pharmacy
8.Nurses
9.[Insert NCA – TBC]
10. EMA - European Medicines Agency
11. Medical Journals
12. Politicians
13. Pharmaceutical companies (including their websites)
14. Another friend or relative (not medically qualified)
15. Social media (e.g. twitter, Facebook)

Q6(a). Have you, personally, ever distrusted a source of information about medicines so much that you chose NOT to take a specific medication?

1. Yes
2. No
3. Don't recall

ASK IF Q6a = 1

Q6(b). You mentioned that your distrust for a source of information about medicines caused you NOT to take a specific medication. Which of the following information sources are you referring to? *(Select all that apply)*

(RANDOMIZE)
1. Patient Advocacy Groups
2. Friends/Family
3. Doctors
4. Nurses
5. Local News
6. National News
7. Internet
8. Newspapers
9. Pharmacists
10. Pharmaceutical Companies
11. Politicians
12. [Insert NCA – TBC]
13. European Medicines Agency
14. Medical Researchers
15. Other *(Specify: _____)*

Q7. How important is each of the following when you decide whether to use a medication? *(Select one per row)*

Very Important	**Somewhat Important**	**Neither Important Nor Unimportant**	**Somewhat Unimportant**	**Very Unimportant**	**Don't Know**

(RANDOMIZE)
1. Trust in sources for health information regarding the specific medication
2. How well the medication works
3. Safety of taking the medication
4. Number of clinical research/trials
5. Whether it can be used in combination with other medications
6. Side effects
7. How frequently I would take the medication
8. Medication form (pill, liquid, injection, etc.)

Q8(a). How effective do you consider the **[UK = NHS, FR = Système de santé Français, SP = , DE =]** are at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?

Very Effective	Fairly Effective	Not Very Effective	Not at all effective	Don't Know

Q8(b) How effective do you consider the **[FOR UK SHOW = UK government, FOR FR SHOW: French Government, FOR DE SHOW: German government, FOR ES SHOW: Spanish government]** are at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?

Very Effective	Fairly Effective	Not Very Effective	Not at all effective	Don't Know

Q9. At what stage do you think information should be conveyed to the public about a possible safety issue of a medicine that they use or may use? (*Please choose one answer only)*

1. When there is a possible sign of a safety problem
2. When the problem has been investigated; not clear if related to the medicine
3. When the problem has been investigated and pharmaceutical company believes it is related to the medicine
4. When the problem has been investigated and regulators believe it is related to medicine

Q9B
Randomise codes 1 - 4
If the information you personally receive (via letter, telephone, email etc…) points to safety problems with **a [Insert specialty group selected @PS2 CODES 1 - 5]** medicine you are currently taking, do you think you are more likely to…

Please choose one answer only

1. Stop taking your medicine

2. Reduce your does of the medicine
3. Continue taking your medicine as usual
4. Seek additional advice about the medicine
5. Don't know

Q10A. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements

Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Don't Know

(RANDOMISE)
1. Patients receiving more information on the safety of medicines would increase their confidence in taking medicines.
2. I am satisfied with the safety information I receive on medicines from regulators
3. As a result of medicines safety incidents I am suspicious about certain medicines

ASK IF 'Strongly Agree' or 'Agree' at Q10A No. 3 'As a result of medicines safety incident I am suspicious about certain medicines'

Q10B. You indicated that you [INSERT response option from Q10A No. 3.] that as a result of medicines safety incidents you are suspicious about certain medicines. Which specific medicines were you referring to?

(Please only state the medicine you indicated)

Now we would like to ask your opinions of two specific organisations. The first concerns [INSERT NCA].

Q11. Have you heard of the **[Insert NCA]** [i.e. MHRA (GB); Bfarm (Germany); ANSM (France); AEMSPS (Spain)]

1. Yes
2. No

Q12. Overall, what is your impression of [INSERT NCA] [MHRA (GB); Bfarm (Germany); ANSM (France); AEMSPS (Spain) Note: put full name in]

The MHRA (Medicines and Healthcare Products Regulatory Agency) is the medicines regulator for the United Kingdom. They are responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe. We are now going to ask you a few questions on your perceptions of how medicines are regulated in the UK.

(SKIP Q.13(a) – 13(b) IF ANSWERED DON'T KNOW FOR NCA AT Q5a AND Q5b]

ASK IF Q5a_11 = 1 – 5

Q13(a). Previously, you mentioned it is **[INSERT RESPONSE FROM Q. 5(a)]** to obtain information about medicines from **[INSERT OPTION 11 SHOWN @Q5a]** Why do you say that? *(Please be as specific as possible)*

ASK IF Q5b_11 = 1 – 4

Q13(b). Previously, you mentioned **[INSERT OPTION 11 SHOWN @Q5b]** is **[INSERT RESPONSE SELECTED @ Q5 (b)]** for information about medicines. Why do you say that? *(Please be as specific as possible)*

SC

Q14(a) Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that **[INSERT OPTION 11 SHOWN @Q5a]** is involved with at the present time?

1. Yes
2. No **(SKIP TO Q15a)**

ASK IF Q14a = 1

Q14(b). What specific pieces of information about medicines or health alerts, or health communication activities the **[INSERT OPTION 11 SHOWN @Q5a]** is involved with at the present time are you aware of? *(Please be as specific as possible)*

ASK IF Q14a = 1 or 2

Q15(a). Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how **[INSERT CODE 11 SELECTED @Q5a]** evaluates medicines.

Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**

(RANDOMISE)
1. I have good knowledge of how **[INSERT OPTION 11 SHOWN @Q5a]** assesses the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
2. **[INSERT OPTION 11 SHOWN @ Q5a]** have the expertise to make competent judgements about **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
3. **[INSERT OPTION 11 SHOWN @ Q5a]** will do what is right for society regarding **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
4. **[INSERT OPTION 11 SHOWN @ Q5a]** will tell the truth about the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
5. **[INSERT OPTION 11 SHOWN @ Q5a]** maintain appropriate distance from the pharmaceutical industry when evaluating **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
6. I believe that the **[INSERT OPTION 11 SHOWN @ Q5a]** will disclose all necessary **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** information to prescribers regarding the risks and benefits of medicines
7. **[INSERT OPTION 11 SHOWN @ Q5a]** communicate openly about its decisions/opinions on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines

ASK IF Q14a = 1 or 2

Q15(b) Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the **[INSERT OPTION 11 SHOWN @Q5]** communicates.

Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**

1. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Medicines" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show**

medicines] information is communicated well to patients by **[INSERT OPTION 11 SHOWN @Q5a]**
2. **[INSERT OPTION 11 SHOWN @Q5]** are a useful source of information on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
3. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Patients" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** patients] find **[INSERT OPTION 11 SHOWN @Q5a]**'s medicines communications comprehensible and understandable
4. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust **[INSERT OPTION 11 SHOWN @Q5a]** to provide me with enough information to prescribe medicines to patients **[SHOW IF dSAMPLE = 1 ONLY]**
5. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust **[INSERT OPTION 11 SHOWN @Q5a]** to provide timely information regarding changes to a medicines safety profile.
6. Too many **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** communications are decided by regulators from **[INSERT OPTION 11 SHOWN @Q5a]** without adequate consultation with those affected

The second set of questions concerns the European Medicines Agency (EMA).

Q16. Have you heard of the European Medicines Agency (EMA)?

1. Yes
2. No

Q17. Overall, what is you impression of the European Medicines Agency (EMA)?

Very Positive	**Fairly Positive**	**Neutral**	**Negative**	**Very Negative**	**Don't Know**	**Have not heard of EMA**

SHOW ALL
The EMA (European Medicines Agency) is a decentralised agency of the European Union. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. We are now going to ask you a few questions on what you think about medicines regulated in Europe.

[SKIP Q18(a) – 18(b) IF ANSWERED DON'T KNOW FOR EMA AT Q5a AND Q5b]

ASK IF Q5a_12 = 1 – 5

Q18(a) Previously, you mentioned it is [**INSERT RESPONSE SELECTED @Q5a for CODE 12**] to obtain information about medicines from EMA. Why do you say that? *(Please be as specific as possible)*

ASK IF Q5a_12 = 1 – 4

Q18(b) Previously, you mentioned EMA is [**INSERT RESPONSE SELECTED @Q5b for CODE 12**] for information about medicines. Why do you say that? *(Please be as specific as possible)*

ASK IF Q17 = 1 – 6

Q19(a). Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that the European Medicines Agency is involved with at the present time?

1. Yes
2. No **(SKIP TO Q. 20)**

ASK IF Q19a = 1

Q19(b) What specific pieces of information about medicines or health alerts, or health communication activities the EMA is involved with at the present time are you aware of? *(Please be as specific as possible)*

Q20(a). Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the EMA evaluates medicines

Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**

(RANDOMISE)
1. I have good knowledge of how EMA assesses the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
2. EMA have the expertise to make competent judgements about **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
3. EMA will do what is right for society regarding **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
4. EMA will tell the truth about the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
5. EMA maintain appropriate distance from the pharmaceutical industry when evaluating **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
6. I believe that the EMA will disclose all necessary **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** information to prescribers regarding the risks and benefits of medicines
7. EMA communicate openly about its decisions/opinions on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
8. EMAs online scientific committee meeting minutes are a useful source of information on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines being evaluated

Q20(b) Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the EMA communicates.

Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**

(RANDOMISE)
1. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Medicines" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** medicines] information is communicated well to patients by EMA

2. EMA are a useful source of information on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
3. Too many **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** communications are decided by regulators from EMA without adequate consultation with those affected
4. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Patients" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** patients] find EMA's medicines communications comprehensible and understandable
5. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust EMA to provide me with enough information to prescribe medicines to patients **[ONLY SHOW IF dSAMPLE = 1]**
6. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust EMA to provide timely information regarding changes to a medicines safety profile

PATIENT DEMOGRAPHICS

Finally, a few questions for classification purposes only.

ASK IF dSAMPLE = 2
SC
PD1. Are you...?

1. Male
2. Female

ASK IF dSAMPLE = 2
SC
ONLY SHOW OPTIONS FOR RELEVANT COUNTRY
PD2. In which of the following regions do you live?

UK
1. North & Yorkshire
2. North West
3. Midlands
4. South West & Wales
5. South East & Anglia
6. London
7. Scotland
8. Northern Ireland

France
1. Region Parisienne
2. Nord-Ouest
3. Nord-Est
4. Sud-Ouest
5. Sud-Est

Spain
1. Noroeste and Noreste
2. Madrid and Centro
3. Este
4. Sur and Canarias

Germany
1. Nielsen I
2. Nielsen II
3. Nielsen IIIa
4. Nielsen IIIb
5. Nielsen IV
6. Nielsen V (a&b)
7. Nielsen VI
8. Nielsen VII

ASK IF dSAMPLE = 2
SC
PD3. And are you...

1. Working 30 hours or more a week (Full-time)
2. Working 8 - 29 hours a week (Part-time)
3. Not working (under 8 hrs) – housewife / houseman
4. Not working (under 8 hrs) – unemployed
5. Not working (under 8 hrs) – unemployed (not Registered but looking for work)
6. Not working (under 8 hrs) – retired
7. Not working (under 8 hrs) – student
8. Not working (under 8 hrs) – other (inc. disabled)

ASK IF dSAMPLE = 2
SC
PD4. Into which of the following categories would you place your total household income from all sources before tax and any other deductions?

1. Under £10,000
2. Over £10,000 but less than £20,000
3. Over £20,000 but less than £30,000
4. Over £30,000 but less than £40,000
5. Over £40,000 but less than £50,000
6. Over £50,000 but less than £75,000
7. Over £75,000
8. Don't know
9. Prefer not to answer

ASK IF dSAMPLE = 2
SC
PD5. Please select the highest educational or professional qualification you have obtained.

1. GCSE / O-level / CSE
2. Vocational qualifications (=NVQ1+2)
3. A-Level or equivalent (=NVQ3)
4. Bachelor Degree or equivalent (=NVQ4)
5. Masters / PhD or equivalent
6. No formal qualifications
7. Still studying
8. Other
9. Don't know

ASK IF dSAMPLE = 2
SC
PD6. Which one of these ethnic groups would you describe yourself as belonging to?

1. White – British
2. White – Irish

3. White – any other white background
4. Asian or Asian British – Indian
5. Asian or Asian British – Pakistani
6. Asian or Asian British – Bangladeshi
7. Asian or Asian British – any other Asian background
8. Black or black British – Caribbean
9. Black or black British – African
10. Black or black British – any other black background
11. Mixed – white and black Caribbean
12. Mixed – white and black African
13. Mixed – white and Asian
14. Mixed – any other mixed background
15. Chinese or other ethnic group – Chinese
16. Chinese or other ethnic group – any other background
17. Prefer not to answer

How long have you been a member of a patient group or organization?

1. Not a member of a patient group
2. Less than a year
3. 1-2 Years
4. 2-5 years
5. 5-10 years
6. 10 years+.

That concludes our survey.
Thank you for participating and sharing your opinions.

Appendix C: Doctor Questionnaire

MEDICAL DOCTOR SCREENER

Thank you for your interest in our study.

This information is being collected for research purposes only. All of the results will be held completely confidentially and only aggregate group findings will be reported.

We would appreciate some information about your practice to determine if the study is appropriate for your medical practice.

In determining whether you are an appropriate candidate for this study, please answer the following questions.

DS 1. What is your primary medical specialty?

	(ALPHABETISED LIST)
1	General Practitioner
2	HIV/AIDS
3	Idiopathic pulmonary fibrosis (IPF)
4	Multiple Sclerosis
5	Osteoporosis
6	Rheumatoid arthritis
7	Other (Please specify)

[If ONLY 'OTHER' SELECTED: TERMINATE]

DS 2. Excluding your residency and fellowship, how many years have you been in practice, post-residency? _____ years.

[If LESS THAN 2 OR MORE THAN 35 YEARS: TERMINATE]

DS 3. Approximately how many hours per week do you work in clinical practice?

_____ [No. of hours].

MEDICAL DOCTOR SCREENER CONTINUED

Please read the following five points carefully before agreeing to participate in this research.

- The aim of this research is to gain your views for academic research and improving healthcare communication only and is not intended to be promotional.
- The identity of respondents is confidential and none of your details will be passed on to any 3rd party.
- Any information you disclose will be treated in the strictest confidence and the results of the research aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to you as an individual.
- You have the right to withdraw from the survey at any time and to withhold information as you see fit
- This survey is supported by a pharmaceutical company.

By proceeding to the next page, please confirm that you have read and understood the points above and are happy to proceed with the market research survey on this basis

(Please put a cross in the box)

TERMINATE TEXT: We're sorry, but you are not eligible to participate in this study. We appreciate your interest and hope that you will participate in future studies. Thank you!!

GENERAL COMMUNICATION OF HEALTH INFORAMTION

The remainder of the survey will take approximately 25 minutes to complete. Just as a reminder, you can stop answering questions and end this survey at any time.

We would first like to ask you some general questions about the communication of health information

Q1. Overall, do you feel that information about medicines and health alerts on issues such as H1-N1/swine flu, food recalls, etc. are communicated to the general public effectively?

3. Yes
4. No

Q2. Would you say that the amount of information about medicines currently publicly available is too much, the appropriate amount, or too little?

4. Too Much
5. Appropriate amount
6. Too Little

Q3. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding **the communication** of information about medicines and health information? *(Select one per row)*

	Agree Strongly	Agree Somewhat	Neither Agree Nor Disagree	Disagree Somewhat	Disagree Strongly	Don't Know
(RANDOMISE)						
5. There is a health information communication process in place to communicate with the general public effectively						
6. Health information is readily available						
7. There are several sources for health information						
8. Health information communicated to the general public is easy to understand						

Q4. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding **information** about medicines and health information? *(Select one per row)*

	Agree Strongly	Agree Somewhat	Neither Agree Nor Disagree	Disagree Somewhat	Disagree Strongly	Don't Know
(RANDOMISE]						
9. Politics affects what health information is communicated to the general public						
10. Health information for the general public is generally unbiased						
11. Health information facts are communicated properly						

12. Health communications generally have consistent information
13. Health communications are generally clear
14. I trust health information from pharmaceutical companies
15. I trust health information from medicines regulators
16. Mainstream media sensationalizes health information

Q5(a). How easy is it for you to obtain information about medicines from each of the following sources?

	Very Easy	**Somewhat Easy**	**Neither Easy Nor Difficult**	**Somewhat Difficult**	**Very Difficult**	**Don't Know**
(RANDOMISE)						
16.	Colleagues **[SHOW IF dSAMPLE = 1 ONLY]**					
17.	Doctors **[SHOW IF dSAMPLE = 2 ONLY]**					
18.	Local hospital					
19.	Summary of Product Characteristics (SmPC) document **[SHOW IF dSAMPLE = 1 ONLY]**					
20.	Internet in general					
21.	Media (e.g. newspapers, television, radio, etc.)					
22.	A medically qualified friend or relative					
23.	Patient advocacy groups					
24.	Pharmacy					
25.	Nurses					
26.	[Insert NCA – TBC]					
27.	EMA - European Medicines Agency					
28.	Medical Journals					
29.	Politicians					
30.	Pharmaceutical companies (including their websites)					
31.	Another friend or relative (not medically qualified)					
32.	Social media (e.g. twitter, Facebook)					

Q5(b). How trustworthy do you believe the following sources are in providing you with advice on the side effects associated with specific medicines?

	Very Trustworthy	**Fairly Trustworthy**	**Neither Trustworthy Nor Untrustworthy**	**Not Very Trustworthy**	**Not at all trustworthy**	**Don't Know**
(RANDOMISE)						
16.	Colleagues **[SHOW IF dSAMPLE = 1 ONLY]**					
17.	Doctors **[SHOW IF dSAMPLE = 2 ONLY]**					
18.	Local hospital					
19.	Summary of Product Characteristics (SmPC) **[SHOW IF dSAMPLE = 1 ONLY]** document					
20.	Internet in general					
21.	Media (e.g. newspapers, television, radio, etc.)					
22.	A medically qualified friend or relative					
23.	Patient advocacy groups					

24.	Pharmacy
25.	Nurses
26.	[Insert NCA – TBC]
27.	~~European Medicines Agency~~ EMA - European Medicines Agency
28.	Medical Journals
29.	Politicians
30.	Pharmaceutical companies (including their websites)
31.	Another friend or relative (not medically qualified)
32.	Social media (e.g. twitter, Facebook) ~~Emergency services (e.g. 999 or 112)~~

Q8(a). How effective do you consider the **[UK = NHS, FR = Système de santé Français, SP = , DE =]** are at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?

Very Effective	Fairly Effective	Not Very Effective	Not at all effective	Don't Know

Q8(b) How effective do you consider the **[FOR UK SHOW = UK government, FOR FR SHOW: French Government, FOR DE SHOW: German government, FOR ES SHOW: Spanish government]** are at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?

Very Effective	Fairly Effective	Not Very Effective	Not at all effective	Don't Know

Q9. At what stage do you think information should be conveyed to the public about a possible safety issue of a medicine that they use or may use? (*Please choose one answer only)*

5. When there is a possible sign of a safety problem
6. When the problem has been investigated; not clear if related to the medicine
7. When the problem has been investigated and pharmaceutical company believes it is related to the medicine
8. When the problem has been investigated and regulators believe it is related to medicine

Q10A. Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements

Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Don't Know

(RANDOMISE)
4. Patients receiving more information on the safety of medicines would increase their confidence in taking medicines.
5. I am satisfied with the safety information I receive on medicines from regulators

6. As a result of medicines safety incidents I am suspicious about certain medicines

ASK IF 'Strongly Agree' or 'Agree' at Q10A No. 3 'As a result of medicines safety incident I am suspicious about certain medicines'

Q10B. You indicated that you [INSERT response option from Q10A No. 3.] that as a result of medicines safety incidents you are suspicious about certain medicines. Which specific medicines were you referring to?

(Please only state the medicine you indicated)

Now we would like to ask your opinions of two specific organisations. The first concerns [INSERT NCA].

Q11. Have you heard of the **[Insert NCA]** [i.e. MHRA (GB); Bfarm (Germany); ANSM (France); AEMSPS (Spain)]

3. Yes
4. No

Q12. Overall, what is your impression of [INSERT NCA]?

Very Positive	**Fairly Positive**	**Neutral**	**Negative**	**Very Negative**	**Don't Know**	**Have not heard of [Insert NCA] [SHOW IF dSAMPLE=1]**

The MHRA (Medicines and Healthcare Products Regulatory Agency) is the medicines regulator for the United Kingdom. They are responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe. We are now going to ask you a few questions on your perceptions of how medicines are regulated in the UK.

(SKIP Q.13(a) – 13(b) IF ANSWERED DON'T KNOW FOR NCA AT Q5a AND Q5b]

Q13(a). Previously, you mentioned it is **[INSERT RESPONSE FROM Q. 5(a)]** to obtain information about medicines from **[INSERT OPTION 11 SHOWN @Q5a]** Why do you say that? *(Please be as specific as possible)*

Q13(b). Previously, you mentioned **[INSERT OPTION 11 SHOWN @Q5b]** is **[INSERT RESPONSE SELECTED @ Q5 (b)]** for information about medicines. Why do you say that? *(Please be as specific as possible)*

Q14(a) Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that **[INSERT OPTION 11 SHOWN @Q5a]** is involved with at the present time?

3. Yes
4. No **(SKIP TO Q15a)**

Q14(b). What specific pieces of information about medicines or health alerts, or health communication activities the **[INSERT OPTION 11 SHOWN @Q5a]** is involved with at the present time are you aware of? *(Please be as specific as possible)*

Q15(a). Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how **[INSERT CODE 11 SELECTED @Q5a]** evaluates medicines.

(RANDOMISE)	**Strongly Agree**	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**
8. I have good knowledge of how **[INSERT OPTION 11 SHOWN @Q5a]** assesses the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
9. **[INSERT OPTION 11 SHOWN @ Q5a]** have the expertise to make competent judgements about **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
10. **[INSERT OPTION 11 SHOWN @ Q5a]** will do what is right for society regarding **[INSERT OPTIONS 2 – 6 FROM DS1 OR**						

OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1] medicines
11. **[INSERT OPTION 11 SHOWN @ Q5a]** will tell the truth about the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
12. **[INSERT OPTION 11 SHOWN @ Q5a]** maintain appropriate distance from the pharmaceutical industry when evaluating **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
13. I believe that the **[INSERT OPTION 11 SHOWN @ Q5a]** will disclose all necessary **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** information to prescribers regarding the risks and benefits of medicines
14. **[INSERT OPTION 11 SHOWN @ Q5a]** communicate openly about its decisions/opinions on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines

Q15(b) Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the **[INSERT OPTION 11 SHOWN @Q5]** communicates.

Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**

7. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Medicines" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** medicines] information is communicated well to patients by **[INSERT OPTION 11 SHOWN @Q5a]**
8. **[INSERT OPTION 11 SHOWN @Q5]** are a useful source of information on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
9. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Patients" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** patients] find **[INSERT OPTION 11 SHOWN @Q5a]**'s medicines communications comprehensible and understandable
10. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust **[INSERT OPTION 11 SHOWN @Q5a]** to provide me with enough information to prescribe medicines to patients **[SHOW IF dSAMPLE = 1 ONLY]**

11. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust **[INSERT OPTION 11 SHOWN @Q5a]** to provide timely information regarding changes to a medicines safety profile.
12. Too many **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** communications are decided by regulators from **[INSERT OPTION 11 SHOWN @Q5a]** without adequate consultation with those affected

SHOW ALL

The second set of questions concerns the European Medicines Agency (EMA).

Q16. Have you heard of the European Medicines Agency (EMA)?

3. Yes
4. No

Q17. Overall, what is you impression of the European Medicines Agency (EMA)?

Very Positive	**Fairly Positive**	**Neutral**	**Negative**	**Very Negative**	**Don't Know**	**Have not heard of EMA**

SHOW ALL

The EMA (European Medicines Agency) is a decentralised agency of the European Union. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. We are now going to ask you a few questions on what you think about medicines regulated in Europe.

[SKIP Q18(a) – 18(b) IF ANSWERED DON'T KNOW FOR EMA AT Q5a AND Q5b]

Q18(a) Previously, you mentioned it is [**INSERT RESPONSE SELECTED @Q5a for CODE 12**] to obtain information about medicines from EMA. Why do you say that? *(Please be as specific as possible)*

Q18(b) Previously, you mentioned EMA is [**INSERT RESPONSE SELECTED @Q5b for CODE 12**] for information about medicines. Why do you say that? *(Please be as specific as possible)*

Q19(a). Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that the European Medicines Agency is involved with at the present time?

3.	Yes
4.	No **(SKIP TO Q. 20)**

Q19(b) What specific pieces of information about medicines or health alerts, or health communication activities the EMA is involved with at the present time are you aware of? *(Please be as specific as possible)*

Q20(a). Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the EMA evaluates medicines

	Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**	**Don't Know**
(RANDOMISE)						
9. I have good knowledge of how EMA assesses the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
10. EMA have the expertise to make competent judgements about **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
11. EMA will do what is right for society regarding **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
12. EMA will tell the truth about the safety of **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
13. EMA maintain appropriate distance from the pharmaceutical industry when evaluating **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
14. I believe that the EMA will disclose all necessary **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** information to prescribers regarding the risks and benefits of medicines						
15. EMA communicate openly about its decisions/opinions on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines						
16. EMAs online scientific committee meeting minutes are a useful source of information on **[INSERT**						

OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1] medicines being evaluated

Q20(b) Please indicate the extent to which you 'agree' or 'disagree' with each of the following statements regarding how the EMA communicates.

Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Don't Know

(RANDOMISE)
7. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Medicines" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** medicines] information is communicated well to patients by EMA
8. EMA are a useful source of information on **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines
9. Too many **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** communications are decided by regulators from EMA without adequate consultation with those affected
10. **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** [**IF CODE 1@ DS1 SHOW** "Patients" **IF INSERTERTING OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM show** patients] find EMA's medicines communications comprehensible and understandable
11. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust EMA to provide me with enough information to prescribe medicines to patients **[ONLY SHOW IF dSAMPLE = 1]**
12. With respect to **[INSERT OPTIONS 2 – 6 FROM DS1 OR OPTIONS 1 – 5 FROM PS2 OR LEAVE BLANK FOR CODE 1 @DS1]** medicines information, I trust EMA to provide timely information regarding changes to a medicines safety profile

MEDICAL DOCTOR DEMOGRAPHICS

Finally, a few questions for classification purposes only.

DD1. Are you . . .?

Male - 1
Female - 2

SCDD2. Which of the following best describes your primary practice?

Solo Practice	- 1
Group Practice	- 2
Clinic	- 3
Hospital	- 4
Other (Please specify)	- 5

ONLY SHOW OPTIONS FOR RELEVANT COUNTRY

DD3. Which of the following best describes the location of your primary practice?

UK

1. North & Yorkshire
2. North West
3. Midlands
4. South West & Wales
5. South East & Anglia
6. London
7. Scotland
8. Northern Ireland

France

1. Region Parisienne
2. Nord-Ouest
3. Nord-Est
4. Sud-Ouest
5. Sud-Est

Spain

1. Noroeste and Noreste
2. Madrid and Centro
3. Este
4. Sur and Canarias

Germany

1. Nielsen I
2. Nielsen II
3. Nielsen IIIa
4. Nielsen IIIb
5. Nielsen IV
6. Nielsen V (a&b)
7. Nielsen VI
8. Nielsen VI

DD4. Which of the following best describes the size of the hospital or surgical centre where you are mainly based?

1. Less than 100 beds
2. 100-299 beds
3. 300-499 beds
4. 500 or more beds
5. Not applicable

DD5. Approximately how many patients **in total** did you treat in the last month?

_____ *(Enter Number of Patients)*

DD6. In your practice, what percent of your <u>total</u> patients are children or adolescents and what percent are adults ages 18 and over?

_____% CHILDREN/ADOLESCENT PATIENTS

_____% ADULT PATIENTS

Total Must = 100%

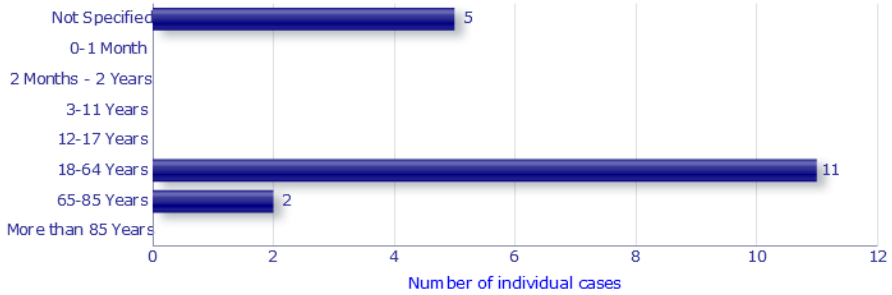
That concludes our survey.
Thank you for participating and sharing your opinions.

Appendix D: Four example screenshots of adrreports.eu for Deltyba (delamanid), a tuberculosis medicine authorised in 2014. Source EMA (2017i)

The number of individual cases identified in EudraVigilance for **DELTYBA** is **18** (up to Feb 2017)

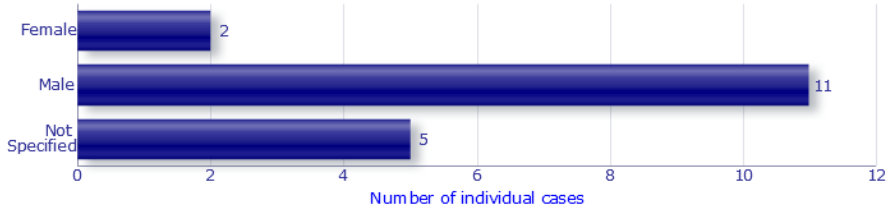
Number of individual cases by Age Group

Age Group	Cases	%
Not Specified	5	27.8%
0-1 Month	0	
2 Months - 2 Years	0	
3-11 Years	0	
12-17 Years	0	
18-64 Years	11	61.1%
65-85 Years	2	11.1%
More than 85 Years	0	
Total	**18**	**100.0%**



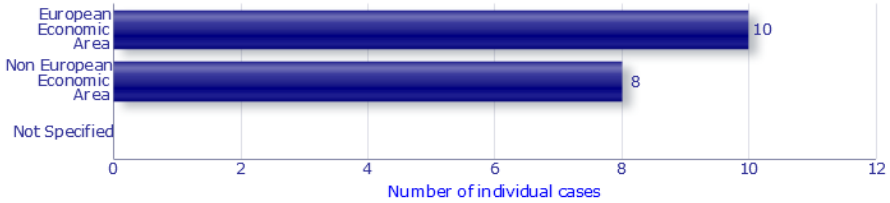
Number of individual cases by Sex

Sex	Cases	%
Female	2	11.1%
Male	11	61.1%
Not Specified	5	27.8%
Total	**18**	**100.0%**



Number of individual cases by Geographic Origin (EEA/Non-EEA)

Occurrence Country EEA/Non EEA	Cases	%
European Economic Area	10	55.6%
Non European Economic Area	8	44.4%
Not Specified	0	
Total	**18**	**100.0%**

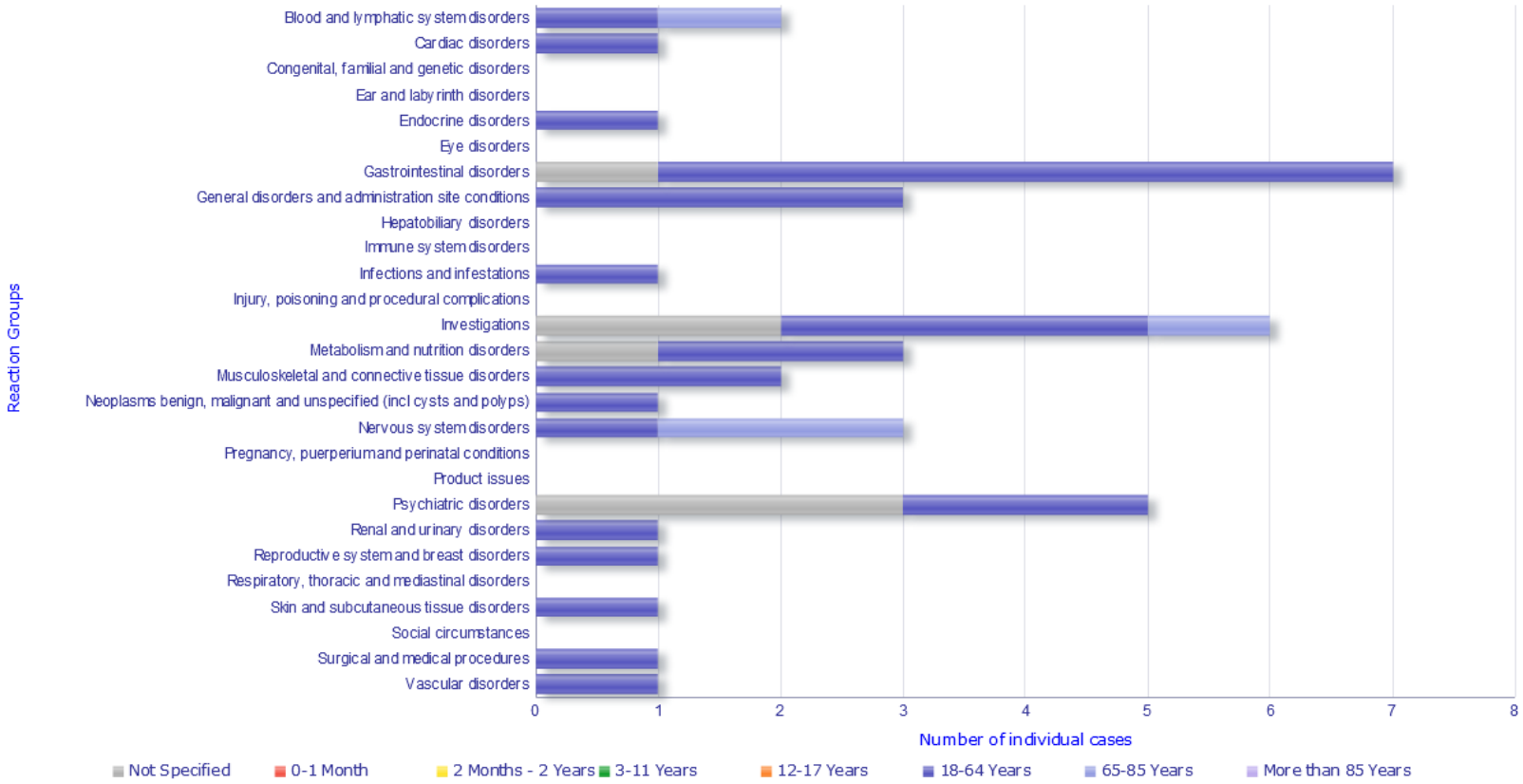


For the interpretation of the results, please refer to the key considerations at www.adrreports.eu

Number of Individual Cases | **Number of Individual Cases By Reaction Groups** | Number of Individual Cases for a selected Reaction Group | Number of Individual Cases for a selected Reaction

By Age Group | By Sex | By Reporter Group | By Geographic Origin

Choose how you want to see the number of individual cases identified in EudraVigilance for **DELTYBA** (up to Feb 2017)



For the interpretation of the results, please refer to the key considerations at www.adrreports.eu

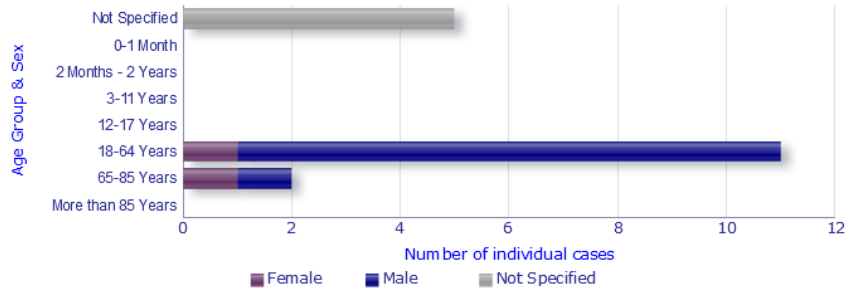
Number of Individual Cases | Number of Individual Cases By Reaction Groups | **Number of Individual Cases for a selected Reaction Group** | Number of Individual Cases for a selected Reaction

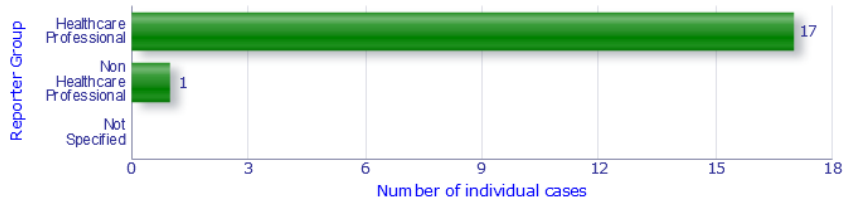
Choose a Reaction Group to see the number of individual cases identified in EudraVigilance for **DELTYBA** (up to Feb 2017)

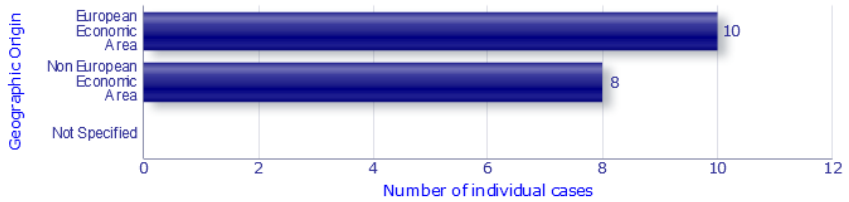
Reaction Groups

- Blood and lymphatic system disorders
- Cardiac disorders
- Endocrine disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Infections and infestations
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Skin and subcutaneous tissue disorders
- Surgical and medical procedures
- Vascular disorders

Number of individual cases by Age Group & Sex, Reporter Group and Geographic Origin







For the interpretation of the results, please refer to the key considerations at www.adrreports.eu

Choose a Reaction Group and then a Reported Suspected Reaction to see the number of individual cases identified in EudraVigilance for **DELTYBA** (up to Feb 2017)

Reaction Groups & Reported Suspected Reaction

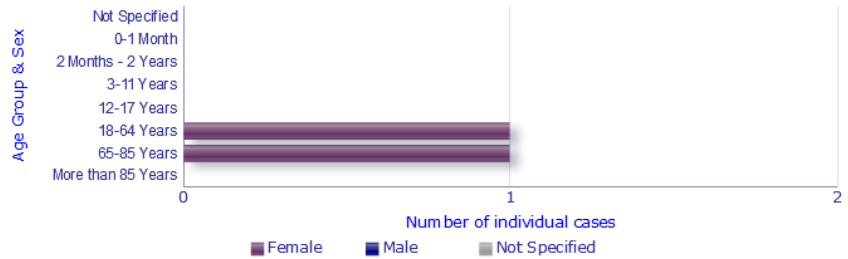
Reaction Groups

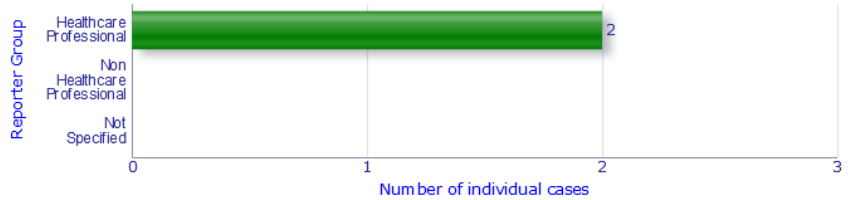
Blood and lymphatic system disorders

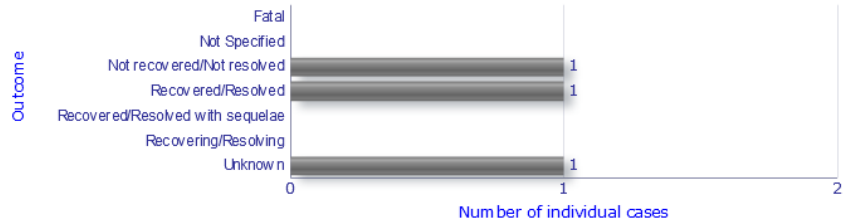
Reported Suspected Reaction

Anaemia
Eosinophilia
Neutropenia

Number of individual cases by Age Group & Sex, Reporter Group and Outcome







For the interpretation of the results, please refer to the key considerations at www.adrreports.eu

Appendix E: Example summary level results document for a vaccine trial that ended in 2007 and was first reported in EU-CTR in 2014.

EU Clinical Trials Register

Clinical trial results:
Immunogenicity and Safety of the Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation (Intramuscular Route)

Summary

EudraCT number	2007-000752-14
Trial protocol	GB
Global end of trial date	03 July 2007
Results information	
Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	03 December 2014

Trial information

Trial identification

Sponsor protocol code	GRT82
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00491257
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43, emmanuel.feroldi@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 58 43, emmanuel.feroldi@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 July 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 July 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To check the compliance, in terms of immunogenicity, of the inactivated, split-virion influenza vaccine Northern Hemisphere 2007-2008 formulation with the requirements of the Committee for Human Medicinal Products (CHMP) Note for Guidance (NfG) CPMP/BWP/214/96.

Protection of trial subjects:

Only subjects who met all the study inclusion and none of the exclusion criteria were vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment were also available on site in case of any immediate allergic reactions.

Background therapy:

Not aplicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 June 2007
Long term follow-up planned	No

Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	88
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled and vaccinated on 11 June 2007 at 2 clinical centers in the United Kingdom.

Pre-assignment

Screening details:

A total of 130 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	18 to 60 years

Arm description:

Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Influenza vaccine (split virion, inactivated)
Investigational medicinal product code	314
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the deltoid muscle, one dose on Day 0

	61 years or older

Arm title

Arm description:

Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Influenza vaccine (split virion, inactivated)
Investigational medicinal product code	314
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the deltoid muscle, one dose on Day 0

Number of subjects in period 1	18 to 60 years	61 years or older	
Started	65	65	

Completed	64	65	
Not completed	1	0	
Lost to follow-up	1	-	

Baseline characteristics

Reporting groups	
Reporting group title	18 to 60 years
Reporting group description: Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.	
	61 years or older
Reporting group title Reporting group description: Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.	

Reporting group values	18 to 60 years	61 years or older	Total
Number of subjects	65	65	130
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	23	88
From 65-84 years	0	42	42
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	40.2	68.1	
standard deviation	± 12.75	± 5.04	-
Gender categorical Units: Subjects			
Female	28	31	59
Male	37	34	71

Previous influenza vaccination Units: Subjects			
Yes	20	51	71
No	45	14	59
Previous influenza infection last winter Units: Subjects			
Yes	3	1	4
No	62	64	126

End points

End points reporting groups

Reporting group title	18 to 60 years

Reporting group description:

Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

	61 years or older

Reporting group title

Reporting group description:

Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

Primary: Summary of Geometric Mean Titers (GMTs) of Influenza Vaccine Antibodies Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route

End point title	Summary of Geometric Mean Titers (GMTs) of Influenza Vaccine Antibodies Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route[1]

End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	65		
Units: Titers				
geometric mean (confidence interval 95%)				
Flu A/SolomonIslands/3/2006 (H1N1; Day 0)	10.9 (8.2 to 14.5)	13.1 (9.86 to 17.3)		
Flu A/Wisconsin/67/2005 (H3N2; Day 0)	24.8 (16.8 to 36.5)	58.1 (38.5 to 87.7)		
Flu B/Malaysia/2506/2004 (B native; Day 0)	7.07 (6.07 to 8.24)	10.3 (8.4 to 12.7)		
Flu B/Malaysia/2506/2004 (B split; Day 0)	11.8 (9.58 to 14.5)	26.2 (20.6 to 33.4)		
Flu A/SolomonIslands/3/2006 (H1N1; Day 21)	311 (221 to 439)	134 (95.9 to 188)		
Flu A/Wisconsin/67/2005 (H3N2; Day 21)	445 (326 to 608)	225 (163 to 310)		
Flu B/Malaysia/2506/2004 (B native; Day 21)	46.2 (34.3 to 62)	24.5 (19.4 to 31)		
Flu B/Malaysia/2506/2004 (B split; Day 21)	116 (96.4 to 139)	74.2 (62.6 to 88)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Geometric Mean Titers Ratios (GMTR) of Influenza Vaccine Antibodies After Vaccination with Inactivated, Split-Virion Influenza Vaccine,
Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route

End point title	Summary of Geometric Mean Titers Ratios (GMTR) of Influenza Vaccine Antibodies After Vaccination with Inactivated, SplitVirion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route[2]

End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Geometric mean titer ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer of antibodies to the influenza virus antigens.

End point type	Primary

End point timeframe:
Day 0 (pre-vaccination) and Day 21 post vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	65		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Flu A/SolomonIslands/3/2006 (H1N1)	28.5 (19.2 to 42.3)	10.3 (7.02 to 15)		
Flu A/Wisconsin/67/2005 (H3N2)	18 (11.5 to 28)	3.87 (2.64 to 5.68)		
Flu B/Malaysia/2506/2004 (B native)	6.53 (4.88 to 8.73)	2.37 (1.93 to 2.91)		
Flu B/Malaysia/2506/2004 (B split)	9.81 (7.32 to 13.1)	2.83 (2.27 to 3.53)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Seroprotection Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular

Route End point title Percentage of Subjects with Seroprotection Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route[3]

End point description:
Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Seroprotection was defined as titers ≥40 (1/dil) on Day 0 and Day 21.

End point type	Primary

End point timeframe:
Day 0 (pre-vaccination) and Day 21 post vaccination

Notes:
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	65		
Units: Percentage of subjects				
number (not applicable)				
Flu A/SolomonIslands/3/2006 (H1N1; Day 0)	19	20		
Flu A/Wisconsin/67/2005 (H3N2; Day 0)	42.9	56.9		
Flu B/Malaysia/2506/2004 (B native; Day 0)	4.8	10.8		
Flu B/Malaysia/2506/2004 (B split; Day 0)	7.9	44.6		
Flu A/SolomonIslands/3/2006 (H1N1; Day 21)	98.4	87.7		
Flu A/Wisconsin/67/2005 (H3N2; Day 21)	98.4	93.8		
Flu B/Malaysia/2506/2004 (B native; Day 21)	60.3	40		
Flu B/Malaysia/2506/2004 (B split; Day 21)	93.7	84.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008

Formulation by Intramuscular Route

End point title: Percentage of Subjects Achieving Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008

~~Formulation by Intramuscular Route~~[4]

~~End point description:~~

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Seroconversion was defined as subjects with a titer <10 (1/dil) on Day 0 and a post-injection titer ≥40 (1/dil) on Day 21 or significant increase was defined as subjects with a titer ≥10 (1/dil) on Day 0 and a ≥4-fold increase from pre- to post-injection titer on Day 21.

End point type	Primary

End point timeframe:

Day 21 post vaccination

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	65		
Units: Percentage of subjects				
number (not applicable)				
Flu A/SolomonIslands/3/2006 (H1N1)	88.9	66.2		
Flu A/Wisconsin/67/2005 (H3N2)	81	36.9		
Flu B/Malaysia/2506/2004 (B native)	54	20		
Flu B/Malaysia/2506/2004 (B split)	81	26.2		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with at Least One Reaction Corresponding to those Listed in the EMEA Recommendation Within 3 Days After Vaccination with
Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by Intramuscular Route

~~End point title~~	~~Percentage of Subjects with at Least One Reaction Corresponding to those Listed in the EMEA Recommendation Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by Intramuscular Route~~[5] ~~End point description:~~

Solicited injection site: Induration and Ecchymosis. Solicited systemic reactions: Temperature, Malaise, and Shivering.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 post-vaccination

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site induration >5 cm for >3 days	0	0		
Injection site ecchymosis	10.9	4.6		
Temperature >38˚C for ≥24 hours	0	0		
Malaise	17.2	6.2		
Shivering	6.3	4.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route

~~End point title~~ ~~Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route~~[6] ~~End point description:~~

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 injection site: Pain –
Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis – ≥5 cm. Grade 3 systemic reactions: Fever – >39.0°C; Headache, Malaise, Myalgia, and Shivering – Prevents daily activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 post-vaccination

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	39.1	24.6		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	9.4	10.8		
Grade 3 Injection site Erythema	1.6	4.6		
Injection site Swelling	12.5	12.3		
Grade 3 Injection site Swelling	1.6	1.5		
Injection site Induration	15.6	9.2		
Grade 3 Injection site Induration	1.6	0		
Injection site Ecchymosis	10.9	4.6		
Grade 3 Injection site Ecchymosis	0	0		
Fever	1.6	0		
Grade 3 Fever	0	0		
Headache	26.6	16.9		
Grade 3 Headache	4.7	1.5		
Malaise	17.2	6.2		
Grade 3 Malaise	1.6	1.5		
Myalgia	23.4	10.8		
Grade 3 Myalgia	1.6	0		
Shivering	6.3	4.6		
Grade 3 Shivering	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions More than 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route

~~End point title~~	~~Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions More than 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2007-2008 Formulation by the Intramuscular Route~~[7] ~~End point description:~~

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 injection site: Pain –
Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis – ≥5 cm. Grade 3 systemic reactions: Fever – >39.0°C; Headache, Malaise, Myalgia, and Shivering – Prevents daily activities.

End point type	Primary

End point timeframe:

>Day 3 post vaccination

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	0	0		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	0	0		
Grade 3 Injection site Erythema	0	0		
Injection site Swelling	0	0		
Grade 3 Injection site Swelling	0	0		

Injection site Induration	0	0		
Grade 3 Injection site Induration	0	0		
Injection site Ecchymosis	0	0		
Grade 3 Injection site Ecchymosis	0	0		
Fever	0	0		
Grade 3 Fever	0	0		
Headache	1.6	0		
Grade 3 Headache	0	0		
Malaise	0	1.5		
Grade 3 Malaise	0	0		
Myalgia	0	3.1		
Grade 3 Myalgia	0	0		
Shivering	0	0		
Grade 3 Shivering	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to Day 21 post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	18 to 60 years

Reporting group description:

Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

	61 years or older

Reporting group title

Reporting group description:

Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2007-2008 formulation on day 0.

Serious adverse events	18 to 60 years	61 years or older	
Total subjects affected by serious adverse events subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	18 to 60 years	61 years or older	
Total subjects affected by non-serious adverse events subjects affected / exposed	25 / 65 (38.46%)	16 / 65 (24.62%)	

Nervous system disorders			
Headache alternative assessment type: Systematic			
subjects affected / exposed[1]	17 / 64 (26.56%)	11 / 65 (16.92%)	
occurrences (all)	17	11	
General disorders and administration site conditions			
Injection site ecchymosis alternative assessment type: Systematic			
subjects affected / exposed[2]	7 / 64 (10.94%)	3 / 65 (4.62%)	
occurrences (all)	7	3	
Malaise alternative assessment type: Systematic			
subjects affected / exposed[3]	11 / 64 (17.19%)	4 / 65 (6.15%)	
occurrences (all)	11	4	
Shivering alternative assessment type: Systematic			
subjects affected / exposed[4]	4 / 64 (6.25%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
Injection site pain alternative assessment type: Systematic			
subjects affected / exposed[5]	25 / 64 (39.06%)	16 / 65 (24.62%)	
occurrences (all)	25	16	
Injection site erythema alternative assessment type: Systematic			
subjects affected / exposed[6]	6 / 64 (9.38%)	7 / 65 (10.77%)	
occurrences (all)	6	7	

Injection site swelling alternative assessment type: Systematic subjects affected / exposed[7] occurrences (all) Injection site induration alternative assessment type: Systematic subjects affected / exposed[8] occurrences (all)	8 / 64 (12.50%) 8 10 / 64 (15.63%) 10	8 / 65 (12.31%) 8 6 / 65 (9.23%) 6	
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed[9] occurrences (all)	15 / 64 (23.44%) 15	7 / 65 (10.77%) 7	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal. Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal. Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal. Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal. Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 3 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Appendix F – Statement on Dominic Way's contribution to research at KCRM

I, Ragnar Löfstedt, and in the capacity of his primary supervisor have written this statement to clarify Dominic Way's contribution to the KCRM research group during his PhD. Before Dominic started his thesis in October 2012, I had already conducted research in the US on the FDA's transparency and risk communication strategy. This resulted in two papers specifically examining transparency policy relating to the Center for Drug Evaluation and Research's (CDER) adverse event reporting system (Löfstedt *et al*. 2011; Chakraborty and Löfstedt, 2012).

Shortly after completing these projects, Dominic asked me during his KCRM Risk Analysis Master's course for recommendations on possible risk communication topics for a PhD proposal. One of the five options I gave him was on the relation between transparency and risk communication and the policies being implemented in different sectors. After discussing what policy domain Dominic might focus on, we agreed that pharmaceuticals and the European Medicines Agency's policies would be ideal: Dominic conducted his Undergraduate and Master's dissertations on healthcare and medicines policy. He subsequently conducted an explorative literature review on transparency and trust in the European pharmaceutical domain that informed a proposal for his PhD. At the same time, a former PhD student of mine, Dr. Bouder (Maastricht University), and I wrote our own paper on transparency in risk regulation that Dominic generously provided comments and suggestions on in late 2012 and early 2013 (Löfstedt and Bouder, 2014).

During the first year of his PhD, Dr. Bouder led a project on antivirals and the swine and avian flu pandemics. After discussions between Dr. Bouder, Dominic and myself, we decided that the results of the project were also highly relevant to understanding the relation between transparency and risk communication. Dominic subsequently led on all data analyses and co-wrote an exploratory paper on transparency in Europe (Bouder, Way, Löfstedt and Evensen 2015). Meanwhile Dominic and I conducted experiments investigating the link between transparency and risk communication in Europe. We designed those experiments together and Dominic carried out all the data collection work in all four sample countries: the UK, the Netherlands, Spain and Germany (Löfstedt and Way, 2016a, 2016b). The results of neither of these studies are reported in Dominic's thesis but did inform his approach to investigating transparency, the type of data he collected, and how. He has discussed this in the methodology chapter (Chapter IV, pp. 95-96).

To aid Dominic in collecting data on EMA' policies, I also connected him with senior EMA staff in November 2012 at the agency's headquarters during what became a milestone workshop on transparency. Following this event, Dominic developed his own networks and contacts in the pharmaceutical domain. This enhanced his understanding of EMA, enabled him to keep up with policy developments, and allowed him to undertake his own research on transparency and risk communication reported in his thesis. Dominic was subsequently invited to and organised elite policy meetings and interviews between 2012 and 2016 (pp. 84-90). Dominic also led on the design and implementation of two survey projects examining the perspectives of European patients and doctors. He led on designing the questionnaires, worked daily with the polling agency we contracted in London Bridge (Ipsos), contacted patient groups, and liaised with his own regulatory contacts in each sample country (e.g. to check translations). After the data had been collected, Dominic then led on all data analyses for both patient and doctor samples. While Dominic led on the longer theory paper and patient results (Way, Bouder, Löfstedt and Evensen, 2016), he also wrote all the results and data analyses for a second paper on the perspectives of doctors (Löfstedt, Way, Bouder and Evensen, 2016).

Dominic then used the survey data to independently carry out further statistical analyses comparing the perspectives of patients and doctors and contextualising the results for his own PhD research agenda. These results are reported in Chapter VII and his personal interpretations of the results are reported in Chapter VIII with no input from the research team.

Dominic's PhD thesis has a total of nine chapters and I can clarify the influence of our research team on each specific chapter.

1. Introduction. 100% Dominic.
2. Typology. 100% Dominic.
3. Literature review. 100% Dominic. While the decision to focus his PhD on transparency and risk communication was influenced by a book chapter written by myself and Dr. Bouder (Löfstedt and Bouder, 2014), his literature review chapter was written entirely separately from the research team.
4. Methodology. 100% Dominic.
5. History of transparency at EMA. 100% Dominic. While Dominic was writing this historical analysis, I wrote a paper separately on the history of transparency at EFSA. A joint paper led by Dominic comparing EMA (Dominic) and EFSA's (Ragnar) transparency policies is currently under review in EJRR (Way and Löfstedt, forthcoming)
6. EMA's three input policies. 100% Dominic.
7. Patient and doctor survey results. As explained above, Dominic led on designing the questionnaires, collecting the results with Ipsos, analysing the data and publishing the results in two journal articles. The subsequent analyses reported in this chapter, comparison of patients and doctors, and interpretation of the data was conducted entirely by Dominic and independently from the rest of the research team.
8. Evaluation of EMA's policies. 100% Dominic.
9. Conclusion and recommendations. The conclusions were 100% Dominic. Recommendations 1 and 2 have been developed by the research team over the years but improved and explained in more detail by Dominic. The rest of the recommendations are 100% Dominic.

Professor Ragnar Löfstedt
27th June, 2017